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ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	15517
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
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ANTISENSEHES.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEION:.DWPI,EPAB,JPAB,USPT,PGPB.	1
(CD81 SAME (ANTISENS$ OR RIBOZYM$ OR ANTIBOD$ OR INHIBIT$)).USPT,PGPB,JPAB,EPAB,DWPI.	24

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DATE: Monday, September 16, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L1	cd81 same (antisens$ or ribozym$ or antibod$ or inhibit$)	24	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 10 of 24 returned.

1. Document ID: US 20020119945 A1

L1: Entry 1 of 24 File: PGPB Aug 29, 2002

PGPUB-DOCUMENT-NUMBER: 20020119945
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020119945 A1

TITLE: Methods for inhibiting proliferation of astrocytes and astrocytic tumor cells and uses thereof

PUBLICATION-DATE: August 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Weinstein, David E.	Dobbs Ferry	NY	US	

US-CL-CURRENT: 514/44; 435/455, 435/458, 435/459

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

2. Document ID: US 20020119495 A1

L1: Entry 2 of 24 File: PGPB Aug 29, 2002

PGPUB-DOCUMENT-NUMBER: 20020119495
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020119495 A1

TITLE: Immunogenic composition of hepatitis C and methods of use thereof

PUBLICATION-DATE: August 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Nakano, Eileen T.	Honolulu	HI	US	
Clements, David E.	Honolulu	HI	US	
Humphreys, Tom	Honolulu	HI	US	

US-CL-CURRENT: 435/7.1; 424/189.1, 424/225.1, 424/228.1, 435/345, 435/5, 435/69.1, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

3. Document ID: US 20020102604 A1

L1: Entry 3 of 24 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102604
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102604 A1

TITLE: Full-length human cDNAs encoding potentially secreted proteins

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Milne Edwards, Jean-Baptiste Dumas	Paris		FR	
Bougueleret, Lydie	Petit Lancy		CH	
Jobert, Severin	Paris		FR	

US-CL-CURRENT: 435/7.1; 530/350, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC
Draw Desc | Image

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4. Document ID: US 20020086034 A1

L1: Entry 4 of 24 File: PGPB Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020086034
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020086034 A1

TITLE: Compositions and methods for treating viral infections

PUBLICATION-DATE: July 4, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Gelder, Frank B.	Shreveport	LA	US	

US-CL-CURRENT: 424/208.1; 424/188.1, 435/339.1, 435/5, 435/6, 435/7.1, 530/300, 530/324, 530/325, 530/326, 530/388.35, 530/389.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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5. Document ID: US 20020078472 A1

L1: Entry 5 of 24 File: PGPB Jun 20, 2002

PGPUB-DOCUMENT-NUMBER: 20020078472
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020078472 A1

TITLE: METHODS AND MEANS FOR EXPRESSION OF MAMMALIAN POLYPEPTIDES IN MONOCOTYLEDONOUS PLANTS

PUBLICATION-DATE: June 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
CHRISTOU, PAUL	COLNEY		GB	
STOGER, EVA	COLNEY		GB	
FISCHER, RAINER	AACHEN		DE	
MARTIN-VAQUERO, CARMEN	COLNEY		GB	
SCHILLBERG, STEFAN	COLNEY		GB	
K-C MA, JULIAN	LONDON		GB	

US-CL-CURRENT: 800/278

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

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6. Document ID: US 20020058029 A1

L1: Entry 6 of 24 File: PGPB May 16, 2002

PGPUB-DOCUMENT-NUMBER: 20020058029
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020058029 A1

TITLE: Combination therapy for treatment of autoimmune diseases using B cell depleting/immunoregulatory antibody combination

PUBLICATION-DATE: May 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	

US-CL-CURRENT: 424/131.1; 424/144.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

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7. Document ID: US 20020028178 A1

L1: Entry 7 of 24 File: PGPB Mar 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020028178
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020028178 A1

TITLE: Treatment of B cell malignancies using combination of B cell depleting antibody and immune modulating antibody related applications

PUBLICATION-DATE: March 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/1.49; 424/143.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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8. Document ID: US 20020012665 A1 Jan 31, 2002

File: PGPB

L1: Entry 8 of 24

PGPUB-DOCUMENT-NUMBER: 20020012665
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020012665 A1

TITLE: Combined use of anti-cytokine antibodies or antagonists and anti-CD20 for treatment of B cell lymphoma

PUBLICATION-DATE: January 31, 2002

INVENTOR-INFORMATION:				
NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	

US-CL-CURRENT: 424/145.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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9. Document ID: US 20020009730 A1 Jan 24, 2002

File: PGPB

L1: Entry 9 of 24

PGPUB-DOCUMENT-NUMBER: 20020009730
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009730 A1

TITLE: Human stress array

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:				
NAME	CITY	STATE	COUNTRY	RULE-47
Chenchik, Alex	Palo Alto	CA	US	
Lukashev, Matvey E.	Newton	MA	US	

US-CL-CURRENT: 435/6; 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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10. Document ID: US 20020006404 A1

L1: Entry 10 of 24 File: PGPB Jan 17, 2002

PGPUB-DOCUMENT-NUMBER: 20020006404
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020006404 A1

TITLE: Treatment of cell malignancies using combination of B cell depleting antibody and immune modulating antibody related applications

PUBLICATION-DATE: January 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/142.1; 424/155.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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CD81S	0
ANTISENS$	0
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ANTISENSC.DWPI,EPAB,JPAB,USPT,PGPB.	8
ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	15517
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSED.DWPI,EPAB,JPAB,USPT,PGPB.	19
ANTISENSEDEOXYOLIGONUCLEOTIDE.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEHES.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEION:.DWPI,EPAB,JPAB,USPT,PGPB.	1
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Search Results - Record(s) 11 through 20 of 24 returned.

11. Document ID: US 20020004587 A1

L1: Entry 11 of 24 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004587
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004587 A1

TITLE: Multivalent antibodies and uses therefor

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Miller, Kathy L.	San Francisco	CA	US	
Presta, Leonard G.	San Francisco	CA	US	

US-CL-CURRENT: 530/388.8; 424/143.1, 435/325, 435/334, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

12. Document ID: US 20020004210 A1

L1: Entry 12 of 24 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004210
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004210 A1

TITLE: CALCIUM-INDEPENDENT NEGATIVE REGULATION BY CD81 OF RECEPTOR SIGNALLING

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
FLEMING, TONY	NEWTON	MA	US	
KINET, JEAN-PIERRE	LEXINGTON	MA	US	

US-CL-CURRENT: 435/7.21; 514/12, 514/2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

13. Document ID: US 20020002272 A1

L1: Entry 13 of 24 File: PGPB Jan 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020002272
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020002272 A1

TITLE: Eliciting HCV-specific antibodies

PUBLICATION-DATE: January 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Houghton, Michael	Danville	CA	US	
Selby, Mark	San Francisco	CA	US	
Abrignani, Sergio	Vagliagli	CA	IT	
Heile, Jens Martin	Ludwigsburg		DE	
O'Hagan, Derek	Berkeley		US	

US-CL-CURRENT: 530/388.3; 424/228.1, 435/320.1, 435/5, 435/7.1, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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14. Document ID: US 20010053770 A1

L1: Entry 14 of 24 File: PGPB Dec 20, 2001

PGPUB-DOCUMENT-NUMBER: 20010053770
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010053770 A1

TITLE: Bispecific molecules cross-linking ITIM and ITAM for therapy

PUBLICATION-DATE: December 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thomas, David	Houston	TX	US	
Tam, Sunny	Missouri City	TX	US	

US-CL-CURRENT: 514/44; 424/450, 435/320.1, 435/366, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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15. Document ID: US 6423501 B2

L1: Entry 15 of 24 File: USPT Jul 23, 2002

US-PAT-NO: 6423501
DOCUMENT-IDENTIFIER: US 6423501 B2

TITLE: Calcium-independent negative regulation by CD81 of receptor signaling

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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16. Document ID: US 6335017 B1

L1: Entry 16 of 24 File: USPT Jan 1, 2002

US-PAT-NO: 6335017
DOCUMENT-IDENTIFIER: US 6335017 B1

TITLE: Compositions and methods for treating viral infections

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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17. Document ID: US 6291239 B1

L1: Entry 17 of 24 File: USPT Sep 18, 2001

US-PAT-NO: 6291239
DOCUMENT-IDENTIFIER: US 6291239 B1

TITLE: Monoclonal antibody

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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18. Document ID: US 6258599 B1

L1: Entry 18 of 24 File: USPT Jul 10, 2001

US-PAT-NO: 6258599
DOCUMENT-IDENTIFIER: US 6258599 B1

TITLE: Compositions and methods for treating viral infections

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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19. Document ID: US 6043347 A

L1: Entry 19 of 24 File: USPT Mar 28, 2000

US-PAT-NO: 6043347
DOCUMENT-IDENTIFIER: US 6043347 A

TITLE: Compositions and methods for treating viral infections

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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20. Document ID: WO 9825647 A1 Jun 18, 1998

L1: Entry 20 of 24 File: EPAB

PUB-NO: WO009825647A1
DOCUMENT-IDENTIFIER: WO 9825647 A1
TITLE: CALCIUM-INDEPENDENT MODULATION BY CD81 OF RECEPTOR SIGNALLING

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC

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ANTISENSC.DWPI,EPAB,JPAB,USPT,PGPB.	8
ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	15517
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSED.DWPI,EPAB,JPAB,USPT,PGPB.	19
ANTISENSEDEOXYOLIGONUCLEOTIDE.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEHES.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEION:.DWPI,EPAB,JPAB,USPT,PGPB.	1
(CD81 SAME (ANTISENS$ OR RIBOZYM$ OR ANTIBOD$ OR INHIBIT$)).USPT,PGPB,JPAB,EPAB,DWPI.	24

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L1: Entry 22 of 24 File: DWPI Aug 20, 2001

DERWENT-ACC-NO: 2001-496986
DERWENT-WEEK: 200175

TITLE: Remedies for hepatitis C containing substances with antiviral effects e.g. antibodies, proteins, sulfated polysaccharides and low-molecular compounds, by inhibiting binding of hepatitis C virus envelope glycoprotein or CD81

Basic Abstract Text (1):
NOVELTY - A substance can inhibit the binding between hepatitis C virus (HVC) and cells with potential HCV infection, cells with expression of CD81, or CD81, is new.

Basic Abstract Text (14):
(xii) a method for screening substances that can inhibit the binding between HCV E2/SN1 protein and cells with HCV infectivity, cells expressing CD81, or CD81 comprising contacting them in the presence or absence of a test substance and comparing their binding, with the substance, protein, cells and CD81 as defined above, e.g. a substance capable of recognizing the protein;

Basic Abstract Text (19):
MECHANISM OF ACTION - Viral envelope glycoprotein inhibitor; CD81 inhibitor.

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Search Results - Record(s) 21 through 24 of 24 returned.

21. Document ID: AU 200176623 A WO 200202631 A1 Jan 14, 2002

L1: Entry 21 of 24 File: DWPI

DERWENT-ACC-NO: 2002-154730
DERWENT-WEEK: 200237

TITLE: Identifying ligands for CD81, useful potentially for treating hepatitis C infection, using the three-dimensional structure of the long extracellular loop

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

22. Document ID: AU 200132267 A WO 200158459 A1 Aug 20, 2001

L1: Entry 22 of 24 File: DWPI

DERWENT-ACC-NO: 2001-496986
DERWENT-WEEK: 200175

TITLE: Remedies for hepatitis C containing substances with antiviral effects e.g. antibodies, proteins, sulfated polysaccharides and low-molecular compounds, by inhibiting binding of hepatitis C virus envelope glycoprotein or CD81

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

23. Document ID: JP 2001519150 W WO 9918198 A1 AU 9893633 A EP 1021534 A1 Oct 23, 2001

L1: Entry 23 of 24 File: DWPI

DERWENT-ACC-NO: 1999-264018
DERWENT-WEEK: 200202

TITLE: Hepatitis C receptor protein CD81

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

24. Document ID: US 6423501 B2 WO 9825647 A1 AU 9855220 A EP 948354 A1 US 20020004210 A1

L1: Entry 24 of 24 File: DWPI Jul 23, 2002

DERWENT-ACC-NO: 1998-348267
DERWENT-WEEK: 200254

TITLE: Modulation of CD81-mediated signal transduction - used for the treatment of e.g. allergic conditions, anaphylactic reactions, autoimmune disorders or bacterial or parasite infections

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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Term	Documents
CD81.DWPI,EPAB,JPAB,USPT,PGPB.	54
CD81S	0
ANTISENS$	0
ANTISENS.DWPI,EPAB,JPAB,USPT,PGPB.	21
ANTISENSC.DWPI,EPAB,JPAB,USPT,PGPB.	8
ANTISENSE.DWPI,EPAB,JPAB,USPT,PGPB.	15517
ANTISENSEAND.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSED.DWPI,EPAB,JPAB,USPT,PGPB.	19
ANTISENSEDEOXYOLIGONUCLEOTIDE.DWPI,EPAB,JPAB,USPT,PGPB.	1
ANTISENSEHES.DWPI,EPAB,JPAB,USPT,PGPB.	1
(CD81 SAME (ANTISENS$ OR RIBOZYM$ OR ANTIBOD$ OR INHIBIT$)).USPT,PGPB,JPAB,EPAB,DWPI.	24

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L1: Entry 23 of 24 File: DWPI Oct 23, 2001

DERWENT-ACC-NO: 1999-264018
DERWENT-WEEK: 200202

TITLE: Hepatitis C receptor protein CD81

Basic Abstract Text (7):
(5) an assay for HCV antibodies present in a serum sample, comprising allowing competitive binding between antibodies in the sample, a known amount of HCV protein and as known amount of a CD81 protein, and measuring the amount of the known HCV protein that binds to the CD81 protein;

Basic Abstract Text (8):
(6) an assay for HCV in a serum sample, comprising allowing competitive binding between antibodies in the sample and a known amount of a CD81 protein, and measuring the amount of CD81 bound;

Basic Abstract Text (18):
USE - The CD81 protein can be used to raise antibodies, which can then be used in the diagnosis or therapy of Hepatitis C virus (HCV) (claimed). The antibodies can be used to prevent the virus binding to patient cells and being internalized (claimed). The CD81 protein can also be used to treat HCV infection (claimed).

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L1: Entry 20 of 24 File: EPAB Jun 18, 1998

DOCUMENT-IDENTIFIER: WO 9825647 A1
TITLE: CALCIUM-INDEPENDENT MODULATION BY CD81 OF RECEPTOR SIGNALLING

Abstract (1):
CHG DATE=19990617 STATUS=O>Calcium-independent CD81 inhibition of IgE-mediated degranulation in mast cells, particularly through the Fc gamma RIII and Fc epsilon RI receptors, is described, as well as methods of inhibiting allergic processes.

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L1: Entry 15 of 24 File: USPT Jul 23, 2002

DOCUMENT-IDENTIFIER: US 6423501 B2
TITLE: Calcium-independent negative regulation by CD81 of receptor signaling

Abstract Text (1):
Calcium independent CD81 inhibition of IgE-mediated degranulation in mast cells, particularly through the Fc.gamma.RIII and FC.epsilon.RI receptors, is described, as well as methods of inhibiting allergic processes.

Brief Summary Text (4):
As described herein, monoclonal antibodies (mAbs) have been isolated which inhibit Fc.epsilon.RI-induced mast cell degranulation. Through protein isolation, peptide sequencing, cloning, and gene expression, CD81 has been identified as a novel inhibitory receptor for Fc.epsilon.RI and Fc.gamma.RIII. Anti-CD81 mAbs also inhibited passive cutaneous anaphylaxis (PCA) reactions, a model of IgE-dependent, mast cell activation in vivo.

Brief Summary Text (5):
The invention pertains to a method of inhibiting cell surface receptor-mediated signaling comprising contacting a cell with an agent which induces CD81-mediated signal transduction. In a particular embodiment, the cell surface receptor is selected from the group consisting of Fc.epsilon.RI and Fc.gamma.RIII. In one embodiment, the method is a calcium independent method.

Brief Summary Text (6):
The invention also relates to a method of inhibiting degranulation comprising contacting a cell with an agent which induces CD81-mediated signal transduction. In one embodiment, degranulation is mediated by the Fc.epsilon.RI receptor. In another embodiment, the method is a calcium independent method.

Brief Summary Text (7):
The invention further relates to a calcium independent method of inhibiting cell surface receptor-mediated signaling in a mammal, such as a human, comprising administering to the mammal an effective amount of an agent which induces CD81-mediated signal transduction. In one embodiment, the cell surface receptor is selected from the group consisting of Fc.epsilon.RI and Fc.gamma.RIII.

Brief Summary Text (8):
The invention also pertains to a method, e.g., a calcium independent method, of inhibiting degranulation induced by a cell surface receptor-mediated signal in a mammal, such as a human, comprising administering to the mammal an effective amount of an agent which induces CD81-mediated signal transduction.

Brief Summary Text (10):
The invention also relates to a calcium independent method of enhancing cell surface receptor-mediated signaling, e.g., Fc.epsilon.RI-mediated signaling and Fc.gamma.RIII-mediated signaling, comprising contacting a cell with an agent which inhibits CD81-mediated signal transduction.

Brief Summary Text (11):
The invention also pertains to a calcium-independent method of enhancing degranulation comprising contacting a cell with an agent which inhibits CD81-mediated signal transduction. For example, degranulation can be mediated by the

Fc.epsilon.RI receptor. The invention also relates to a calcium independent method of enhancing cell surface receptor-mediated signaling in a mammal comprising administering to the mammal an effective amount of an agent which inhibits CD81-mediated signal transduction.

Drawing Description Text (10):
FIGS. 9A-9C are graphs showing that CD81 mAbs fail to inhibit Fc.epsilon.RI-induced tyrosine phosphorylation, calcium mobilization, and leukotriene synthesis. FIG. 9A shows the effect of anti-CD81 on calcium mobilization of fura-2-loaded RBL-2H3 cells triggered through Fc.epsilon.RI as measured by confocal microscopy. Fluo-3 fluorescence per ml .sup.3 H measurements were normalized by dividing the average fluorescence intensity (F) occurring during the course of the experiment to the average flourescence intensity at the beginning of the experiment (F.sub.0) and expressed as F/F.sub.0. Traces are shown of 10 individual cell (thin lines) together with mean values for these cells (thick lines) and represent typical results obtained from five separate experiments. FIG. 9B shows .sup.3 H-serotonin release from RBL-2H3 cells prepared as in confocal microscopy measurements except that 3 .mu.Ci/ml .sup.3 H-serotonin was added to cultures. FIG. 9C shows LTC.sub.4 measurements from 106 anti-DNP IgE saturated RBL-2H3 treated with 1 .mu.g 5D1 (open squares) or buffer (open circles) prior to triggering with 30 ng/ml DNP-HSA for the indicated periods of time.

Drawing Description Text (11):
FIGS. 10A-10B are graphs showing inhibition of passive cutaneous anaphylaxis in Wistar rats by anti-CD81. Male Wistar rats were injected with (FIG. 10A) 25 ng DNP-specific IgE mixed with 50 .mu.g anti-CD81 mAb 5D1 (mouse IgG1) or control mouse IgG1 mAb (MOPC 31c, specificity unknown) or (FIG. 10B) 100 ng DNP-specific IgE alone. Statistical significance was determined using an unpaired Student's t-test: *, $p<0.05$; **, $p<0.01$ (actual values 10A, $p=0.024$ versus MOPC 31c controls; 10B, $p=0.009$ versus anti-LFA-10 controls).

Drawing Description Text (13):
FIG. 12 is a set of graphs illustrating that DNP-HSA induces IgE-mediated degranulation in four different cell lines and that this degranulation is inhibitable by anti-CD81 mAb 5D1.

Detailed Description Text (18):
Clustering of the high affinity IgE receptor (Fc.epsilon.RI) by antigen initiates a signaling cascade characterized by tyrosine kinase activation, calcium release and influx and, later, by degranulation and release of inflammatory mediators. In order to examine how Fc.epsilon.RI signaling is negatively regulated, a panel of monoclonal antibodies to mast cell membrane antigens was generated and screened for inhibition of IgE-mediated mast cell degranulation. Two degranulation inhibitory antibodies, designated 1A12 and 5D1, immunoprecipitated a Mr 25 kd protein from surface-iodinated rat basophilic leukemia (RBL-2H3) cells. Lys-C peptide sequence obtained from 1A12-immunoaffinity purified immunoprecipitates was found to be highly homologous to mouse and human CD81. Subsequent cloning and expression of rat CD81 cDNA from RBL-2H3 confirmed that 1A12 and 5D1 recognize rat CD81 and that CD81 crosslinking inhibits Fc.epsilon.RI-mediated mast cell degranulation.

Detailed Description Text (19):
Signaling through the high affinity receptor for immunoglobulin E (Fc.epsilon.RI) results in the coordinate activation of tyrosine kinases prior to calcium mobilization. Receptors capable of interfering with the signaling of antigen receptors, such as Fc.epsilon.RI, recruit tyrosine and inositol phosphatases that results in diminished calcium mobilization. It is shown herein that antibodies recognizing CD81 inhibit Fc.epsilon.RI-mediated mast cell degranulation but, surprisingly, without affecting aggregation-dependent tyrosine phosphorylation, calcium mobilization, or leukotriene synthesis. Furthermore, CD81 antibodies also inhibit mast cell degranulation in vivo as measured by reduced passive cutaneous anaphylaxis responses. These results reveal an unsuspected calcium-independent pathway of antigen receptor regulation which is accessible to engagement by membrane proteins and on which novel therapeutic approaches to allergic diseases can be based.

Detailed Description Text (21):
CD81 is broadly expressed on hematopoietic cells (T and B lymphocytes, granulocytes, monocytes) and on some non-lymphoid tumors. The function of CD81 (or other TM4SF proteins) is incompletely understood, although CD81 appears to modulate the signaling of other membrane receptors. CD81 is found in the CD19/CD21 complex on B cells, and mAbs to CD81 or CD19 have been reported to reduce the threshold for B cell receptor signaling (Fearon and Carter, Annu. Rev. Immunol. 13:127-149 (1995)) and enhance B cell adhesion via VLA4 (Behr and Schriever, J. Exp. Med. 182:1191-1199 (1995)). Consistent with a costimulatory role in B cell receptor signaling, CD81 -/- mice express lower levels of CD19 on B cells which is proposed to contribute to a defect in humoral immunity (Maecker and Levy, J. Exp. Med. 185:1505-1510 (1997)). For T lineage cells, both stimulatory and inhibitory activities for anti-CD81 mabs have been reported (Secrist et al., Eur. J. Immunol. 26:1435-1442 (1996); Todd et al., J. Exp. Med. 184:2055-2060 (1996); Oren et al., Mol. Cell. Biol. 10:4007-4015 (1990); and Boismenu et al., Science 271:198-200 (1996)). CD81 ligation enhances IL-4 production from antigen-specific CD4+ T cells (Secrist et al., Eur. J. Immunol. 26:1435-1442 (1996)) and integrin activation and IL 2-dependent proliferation in human thymocytes (Todd et al., J. Exp. Med. 184:2055-2060 (1996)). Alternatively, CD81 was originally called TAPA-1 (target of antiproliferative antibody) based on inhibition of proliferation in human B cell lines by CD81 antibodies (Oren et al., Mol. Cell. Biol. 10:4007-4015 (1990)). Some of these pleiotropic effects may stem from the potential signaling molecules with which CD81 has been reported to associate including CD4, CD8, MHC class II, other TM4SF proteins, integrin VLA4, and phosphatidylinositol 4-kinase (Wright and Tomlinson, Immunol. Today 15:588-594 (1994); Imai et al., J. Immunol. 155:1229-1239 (1995); Angelisova et al., Immunogenetics 39:249-256 (1994); Mannion et al., J. Immunol. 157:2039-2047 (1996); and Berditchevski et al., J. Biol. Chem. 272:2595-2598 (1997)).

Detailed Description Text (22):
Mast cell Fc.epsilon.RI can be saturated with monoclonal IgE antibodies. In the absence of crosslinking by appropriate antigen, IgE binding to Fc.epsilon.RI does not activate mast cells. Monoclonal antibodies are purified from culture supernatants or mouse ascitic fluid (produced by injection of antibody-producing cells into immunocompromised mice by standard techniques, such as those described in Kohler and Milstein, Nature 256:495-497 (1975); Kozbar et al., Immunology Today 4:72 (1983); and Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96 (1985)). Crosslinking by the antigen (protein binding to the IgE) normally induces cell degranulation which can be quantitated by enzyme assay or radioactivity release assay. Antibody treatment of CD81 mast cells inhibits IgE-mediated degranulation; 20 ng of 5D1 monoclonal antibody per 10.sub.5 RBL-2H3 cells inhibits degranulation through IgE-mediated channels by greater than 75%.

Detailed Description Text (23):
Mast cells are a major cell in allergic reactions. Thus, the present invention can be used to develop agents, e.g., antibodies, which inhibit the allergic process, as well as to develop compounds for the treatment of allergies, anaphylactic reactions and related diseases. Agents can also be developed which mimic the process of CD81-mediated inhibition of mast cell degranulation. Anti-CD81 antibodies are more inhibitory than antibodies to other different proteins for IgE-mediated degranulation, particularly because anti-CD81 antibodies act directly and do not require secondary reagents. The work described herein can also be used to develop model systems for the study of activation of mast cells through the Fc.epsilon.RI receptor and to improve the therapeutic capability to modulate the function of these cells.

Detailed Description Text (24):
Agents described herein can be anything which binds to or interacts with CD81 and induces (i.e., activates) or enhances CD81-mediated signal transduction. For example, the agent can be a small molecule, a peptide, or a polyclonal or monoclonal antibody, such as an anti-CD81 antibody. In particular embodiments, the antibody is 5D1 or 1A12.

Detailed Description Text (26):
The protein recognized by the degranulation-inhibitory 5D1 mAb was then identified. 5D1 and a second degranulation-inhibitory mAb (1A12) recognized proteins of Mr 25

kDa. 5D1 and 1A12 blocked each others' binding to RBL-2H3 cells, although neither mAb inhibited IgE binding and, conversely saturation of Fc.epsilon.RI with IgE had no effect on 1A12 binding, suggesting that 1A12 and 5D1 recognized the same protein (see FIG. 8) and that Fc.epsilon.RI and the 1A12/5D1 antigen were not co-localized on the cell membrane. Since mAb 1A12 was more effective at immunoprecipitation and on Western blots, it was used for protein purification. Batch preparations of RBL-2H3 extracts were immunoprecipitated with mAb 1A12, resolved on preparative SDS-PAGE and transferred to nitrocellulose for protein sequencing. Peptide sequence obtained from Lys-C digests of 1A12 immunoprecipitates is shown aligned with homologous sequences from mouse and human CD81 in FIG. 5. Based on these data, rat CD81 was cloned from a RBL-2H3 cDNA library using mouse CD81 cDNA as a probe and expressed in the mouse mast cell line C1.MC/C57.1 (Young et al., Proc. Natl. Acad, Sci. USA 84:9175-9179 (1987)). FACS profiles of C1.MC/C57.1 transfectants are shown in FIG. 8; both degranulation-inhibitory mAbs 1A12 and 5D1 recognized rat CD81.

Detailed Description Text (27):
To target the site of CD81 inhibition of degranulation, the effect of CD81 antibodies on the earliest events of Fc.epsilon.RI signal transduction, i.e. tyrosine phosphorylation of proteins by activated, nonreceptor tyrosine kinases including Lyn and Syk, and calcium mobilization (Jouvin et al., J. Biol. Chem. 269:5918-5925 (1994); Penhallow et al., J. Biol. Chem. 270:23362-23365 (1995); Scharenberg et al., EMBO J. 14:3385-3394 (1995); Lin et al., Cell 85:985-995 (1996)) was examined. In these experiments, IgE-saturated RBL-2H3 cells were pretreated with purified anti-CD81 prior to triggering with DNP-HSA for the indicated periods of time, followed by extraction and immunoprecipitation of total tyrosine-phosphorylated proteins. No major changes in the pattern of Fc.epsilon.RI-induced tyrosine phosphorylation were detected with anti-CD81 treatment prior to antigen triggering. Incubation of RBL-2H3 cells with 5D1 alone (no antigen triggering) did not induce detectable tyrosine phosphorylation.

Detailed Description Text (28):
The effect of anti-CD81 on Fc.epsilon.RI-induced calcium mobilization was monitored on individual, adherent RBL-2H3 cells by confocal microscopy in cells loaded with calcium dye fluo-3. As shown in FIG. 9A, no inhibition of Fc.epsilon.RI-induced calcium mobilization in anti-CD81 treated versus controls was observed by confocal microscopy, despite inhibition of degranulation under these conditions (FIG. 9B). Anti-CD81 pretreatment had no effect on calcium release from intracellular stores in cells triggered in Ca.sup.2+ -free buffer containing 0.5 mM EGTA or on pre-triggering baseline values. Similar results were also obtained with RBL-2H3 triggered through Fc.epsilon.RI in suspension using a spectrophotometer. In separate experiments, anti-CD81 mAb 5D1 did not inhibit leukotriene C.sub.4 (LTC.sub.4) production induced by DNP-HSA/IgE stimulation (FIG. 9C). LTC4 production is dependent on activation of phospholipase A2 (tyrosine kinase and calcium-dependent) and is regulated by PMA-sensitive, protein kinase C isozymes (Currie et al., Biochem. J. 304:923-928 (1994)); Ali et al., J. Immunol. 153:776-788 (1994)). These data suggest that CD81 acts independently of early tyrosine phosphorylation and calcium mobilization events which are critical for mast cell degranulation.

Detailed Description Text (30):
CD81 differs from these inhibitory receptors in three important ways. First, unlike other inhibitory receptors, CD81 inhibits Fc.epsilon.RI-mediated degranulation while leaving both tyrosine phosphorylation and calcium mobilization apparently unaffected. While these results cannot exclude a very selective inhibition of kinase activity by CD81 antibodies, it is clear that no detectable effect is found on tyrosine kinase-sensitive calcium mobilization of LTC.sub.4 production. Second, CD81 belongs to a different structural class of proteins than the other inhibitory receptors. CD81 is a TM4SF protein with four transmembrane spanning segments, two extracellular loops, two short cytoplasmic tails, and a short intracellular loop between transmembrane segments 2 and 3 (Wright and Tomlinson, Immunol. Today 15:588-594 (1994)). Third, the cytoplasmic tails of CD81 lack ITIM motifs. While there is an ITIM-like sequence (GCYGAI) in the short intracellular loop between transmembrane segments 2 and 3, there is no evidence that this site is phosphorylated by tyrosine kinases or capable of binding to SH2 domains.

Detailed Description Text (31):

In order to assess the activity of anti-CD81 in Fc.epsilon.RI signaling in normal mast cells, the passive cutaneous anaphylaxis (PCA) model, a classic system for studying mast cell activation in vivo (Wershil et al., J. Immunol. 154:1391-1398 (1995); Dombrowicz et al., J. Clin. Invest. 99:915-925 (1997)), was chosen. In these experiments, rats were injected intradermally with IgE mixed with anti-CD81 mAb 5D1 (IgG1) or with class-matched mouse (IgG1) as control (FIG. 10A). Additional rats received anti-DNP IgE alone into the skin at time 0, followed by a second injection (buffer, 5D1, or anti-rat LFA-1.beta. (IgG1)) (FIG. 10B) into IgE-injected sites 21 hours after IgE injections. Twenty four hours after IgE priming, rats received 1 mg of antigen intravenously (DNP-HSA containing 1% Evan's blue dye). Mast cell activation through Fc.epsilon.RI in PCA results in the release of several vasoactive substances which act to increase vascular permeability, a property which is quantified by local accumulation of the Evan's blue dye from the vasculature into the sites of IgE injections. These results are expressed as .mu.g Evan's blue converted from A.sub.610 measurements of formamide-extracted tissue biopsies (Dombrowicz et al., J. Clin. Invest. 99:915-925 (1997)). As shown in FIG. 10A, coinjection of anti-CD81 mAb 5D1 during IgE priming significantly inhibited IgE-dependent PCA reactions (p=0.024) compared to class-matched controls.

Detailed Description Text (32):
To limit the possibility of non-specific suppression of PCA reactions due to tissue deposition of IgG.sub.1 mAbs, these experiments were repeated by injecting anti-CD81 mAb 5D1 or anti-LFA-1.beta. (CD18) into the IgE-injected sites 3 hours before antigen administration. LFA-1.beta. is expressed on mast cell lines including RBL-2H3 but anti-LFA-1.beta. has no effect on Fc.epsilon.RI-mediated degranulation in RBL-2H3 cells (Weber et al., Scand. J. Immunol. 45:471-481 (1997)). Similar to coinjection of IgE and IgG.sub.1 mAbs, separate injections of anti-CD81 yielded significant inhibition of PCA reactions compared to anti-LFA-1.beta. controls (FIG. 10B).

Detailed Description Text (33):
Thus, it is demonstrated herein that CD81 is a novel inhibitory receptor for Fc.epsilon.RI. The observation that CD81 acts on calcium-independent events required for mast cell degranulation distinguishes CD81 from previously described inhibitory receptors, such as Fc.gamma.RIIb1 and KIR, which act upstream of calcium influx. Anti-CD81 mAbs also inhibited IgE-dependent PCA reactions, which suggests the CD81 pathway is present in normal mast cells and capable of being engaged to inhibit mast cell responses in vivo. Therefore, the CD81 inhibitory pathway can be utilized in therapeutic strategies aimed at intervention of allergic responses.

Detailed Description Text (34):
RBL-2H3 cells express Fc.epsilon.RI, CD81 and endogenous rat Fc.gamma.RIII receptors. However, no high-affinity reagent (antibody) is available to trigger the Fc.gamma.RIII receptors on RBL-2H3; the 2.4G2 antibody (anti-mouse Fc.gamma.RII/Fc.gamma.RIII) was used for this purpose. To demonstrate that CD81 stimulation inhibits degranulation induced through Fc.gamma.RIII signaling as it does for Fc.epsilon.RI, murine Fc.gamma.RIII.alpha. chain cDNA was expressed in RBL-2H3 cells.

Detailed Description Text (35):
Fc.gamma.RIII binding of IgG is detectable only when IgG is present in the form of IgG-containing immune complexes which crosslink Fc.gamma.RIII receptors and initiate intracellular signals. One of the methods of triggering Fc.gamma.RIII is through stimulation with crosslinked anti-Fc.gamma.RIII antibodies. FIG. 12 shows the results when RBL-2H3 and Fc.gamma.RIII-transfectants of RBL-2H3 were loaded with .sup.3 H-serotonin in the presence (DNP-HSA stimulation) or absence (immune complex stimulation) of DNP-specific IgE. After overnight incubation, cells were washed and incubated with culture media or media containing 200 ng of anti-rat CD81 mAb 5D1 prior to triggering with optimized concentrations of DNP-HSA or with preformed immune complexes of 2.4G2/anti-rat IgG F(ab').sub.2. Degranulation was allowed to proceed for 30 minutes at 37.degree. C. and released .sup.3 H-serotonin was quantitated by scintillation counting. As shown in FIG. 12, DNP-HSA induces IgE-mediated degranulation in all four cell lines which is inhibitable by anti-CD81 mAb 5D1. 2.4G2/anti-rat IgG F(ab')2 preformed complexes, but not anti-rat IgG F(ab)2 alone, induce degranulation only in cells expressing mFc.gamma.RIII receptors

(RBL-2H3 transfectants A10, D10 and H11), a process which is also inhibitable by preincubation with 5D1. This data provides the identification of CD81 as a common inhibitor of both Fc.epsilon.RI and Fc.gamma.RIII.

Detailed Description Text (36):
Accordingly, the present invention relates to a method of inhibiting or enhancing cell surface receptor signaling, e.g., Fc.epsilon.RI-mediated or Fc.gamma.RIII-mediated signaling. The method of inhibiting cell surface receptor signaling comprises contacting a cell with an effective amount of an agent which enhances or induces CD81-mediated signal transduction. Alternatively, the method can be a method of inhibiting cell surface receptor signaling in a mammal, comprising administering to the mammal an effective amount of an agent which enhances or induces CD81-mediated signal transduction. Appropriate cells are any cell type which expresses or has been designed to express (e.g., by transfection or genetic engineering) both CD81 and a suitable cell surface receptor.

Detailed Description Text (38):
The method of enhancing cell surface receptor signaling comprises contacting a cell with an effective amount of an agent which inhibits or prevents CD81-mediated signal transduction. Alternatively, the method can be a method of enhancing cell surface receptor signaling in a mammal, comprising administering to the mammal an effective amount of an agent which inhibits or prevents CD81-mediated signal transduction. It may be clinically beneficial to enhance cell surface receptor signaling in a mammal, or the functional results thereof, such as degranulation, in conditions where an inflammatory response and/or release of leukotrienes and cytokines is beneficial, such as in host defense against parasites and bacteria.

Detailed Description Text (40):
As used herein, "inhibit" is intended to encompass any qualitative or quantitative reduction in a measured effect or characteristic, including complete prevention, relative to a control. As also used herein, "enhance" is intended to encompass any qualitative or quantitative increase in a measured effect or characteristic relative to a control. An "effective amount" of a given agent is intended to mean an amount sufficient to achieve the desired effect, e.g., the desired therapeutic effect, under the conditions of administration, such as an amount sufficient for inhibition or enhancement of CD81-mediated signal transduction.

Detailed Description Text (41):
The present invention also relates to preparations for use in the inhibition or enhancement of cell surface receptor signaling, and the treatment of allergic diseases and inflammatory disorders, the preparation including an inhibitor or promoter of CD81-mediated signal transduction, together with a physiologically acceptable carrier and optionally other physiologically acceptable adjuvants.

Detailed Description Text (42):
According to the method, a therapeutically effective amount of one or more agents (e.g., a preparation comprising an inhibitor or promoter of CD81-mediated signal transduction can be administered to an individual by an appropriate route, either alone or in combination with another drug.

Detailed Description Text (46):
The invention also pertains to assays for identifying agents which enhance or inhibit calcium independent CD81-mediated signal transduction. The assay comprises combining a cell bearing CD81 with an agent to be tested, under conditions suitable for signal transduction by CD81. The level or extent of CD81-mediated signal transduction can be measured using standard methods and compared with the level or extent of CD81-mediated signal transduction in the absence of the agent (control). An increase in the level or extent of CD81-mediated signal transduction relative to the control indicates that the agent is a promoter of CD81-mediated signal transduction; a decrease in the level or extent of CD81-mediated signal transduction relative to the control indicates that the agent is an inhibitor of CD81-mediated signal transduction.

Detailed Description Text (47):
Inhibitors or promoters of CD81-mediated signal transduction, e.g., those identified

by methods described herein, can be assessed to determine their effect on cell surface receptor signaling. Inhibitors or promoters of CD81-mediated regulation of cell surface receptor signaling can be, for example, small molecules, antibodies and/or peptides. A cell bearing CD81 and an appropriate cell surface receptor (e.g., Fc.epsilon.RI or Fc.gamma.RIII) are combined with an inhibitor or promoter of CD81-mediated signal transduction under conditions suitable for signal transduction by both CD81 and the cell surface receptor. The level or extent of cell surface receptor signaling can be measured using standard methods and compared with the level or extent of cell surface receptor signaling in the absence of the inhibitor or promoter (control). An increase in the level or extent of cell surface receptor signaling relative to the control indicates that the agent is a promoter of cell surface receptor signaling; a decrease in the level or extent of cell surface receptor signaling relative to the control indicates that the agent is an inhibitor of cell surface receptor signaling.

Detailed Description Text (55):
From 3 separate fusions, a total of 2160 wells were plated and 622 supernatants from wells with hybridoma growth were screened by FACS for reactivity with RBL-2H3 cells. In all, 283/622 (45%) elicited detectable reactivity by FACS with membrane antigens of RBL-2H3. The screening of RBL-2H3-reactive mAbs by serotonin release assay lead to the identification of 1A12 (IgG.sub.2b) and 5D1 (IgG.sub.1), which were characterized further. Rat CD81 transfectants of were stained with purified 1A12 and 5D1 (1 .mu.g/10.sup.6 cells), counterstained with goat anti-mouse F(ab').sub.2 -specific antibody and analyzed by flow cytometry on a FACScan.RTM. flow cytometer.

Detailed Description Text (60):
RBL-2H3 cells were cultured in routine culture medium in spinner flasks to a cell density of approximately 10.sup.6 /ml, harvested by centrifugation and washed twice with cold PBS. Washed cells were extracted in 0.5 M K.sub.2 HPO.sub.4 (pH 7.5) with proteinase inhibitors (10 .mu.g/ml pepstatin, 5 .mu.g/ml leupeptin, and 10 .mu.g/ml aprotinin) at 50.times.10.sup.6 /ml for 60 minutes at 4.degree. C. with frequent mixing. N-octyglucoside (10 mM) was added during the extraction to ensure protein solubility. Post-nuclear lysates were prepared by centrifugation at 15,000.times.g for 20 minutes at 4.degree. C. Lysates were then passed through 0.2 mM filters to remove residual debris and passed several times over protein G-Sepharose coupled to 1A12 (2 mg/ml bed volume), washed with PBS (10 mM n-octylglucoside) and eluted with 0.2 M glycine. Tris-neutralized, concentrated extracts were reduced with .beta.-mercaptoethanol, resolved on 12.5% preparative SDS-PAGE and transferred to Immobilon.sup.SQ (Millipore, Bedford, Mass.). The membrane was stained with amido black and the Mr 25 kDa band was excised, eluted, alkylated and digested overnight with Lys-C. Peptides were separated by reverse phase-HPLC and the peptide peak eluting at 36 minutes was sequenced. Subsequent cloning and expression of rat CD81 cDNA from RBL-2H3 confirmed that 1A12 and 5D1 recognize rat CD81 and that CD81 crosslinking inhibits Fc.epsilon.RI-mediated mast cell degranulation.

Detailed Description Text (69):
RBL-2H3 cells express Fc.epsilon.RI, CD81 and endogenous rat Fc.gamma.RIII receptors. However, no high-affinity reagent (antibody) is available to trigger these receptors on RBL-2H3; the 2.4G2 antibody (anti-mouse Fc.gamma.RII/Fc.gamma.RIII) was used for this purpose. To demonstrate that CD81 stimulation inhibits degranulation induced through Fc.gamma.RIII signaling as it does for Fc.epsilon.RI, murine Fc.gamma.RIII.alpha. chain cDNA was expressed in RBL-2H3 cells. FcR.gamma. cDNA was cotransfected to assist in the surface expression of Fc.gamma.RIII complexes. In FIGS. 11A-11D, the histograms of 3 stable mouse Fc.gamma.RIII RBL-2H3 transfectants are shown after staining with 2.4G2 and FITC-anti-rat IgG. Untransfected RBL-2H3 cells exhibit no detectable binding of 2.4G2 (FIG. 11A).

Detailed Description Text (70):
Fc.gamma.RIII binding of IgG is detectable only when IgG is present in the form of IgG-containing immune complexes which crosslink Fc.gamma.RIII receptors and initiate intracellular signals. One of the methods of triggering Fc.gamma.RIII is through stimulation with crosslinked anti-Fc.gamma.RIII antibodies. In FIG. 12, RBL-2H3 and Fc.gamma.RIII-transfectants of RBL-2H3 were loaded with .sup.3 H-serotonin in the presence (DNP-HSA stimulation) or absence (immune complex stimulation) of

DNP-specific IgE. After overnight incubation, cells were washed and incubated with culture media or media containing 200 ng of anti-rat CD81 mAb 5D1 prior to triggering with optimized concentrations of DNP-HSA or with preformed immune complexes of 2.4G2/anti-rat IgG F(ab').sub.2. Degranulation was allowed to proceed for 30 minutes at 37.degree. C. and released .sup.3 H-serotonin was quantitated by scintillation counting. As shown in FIG. 12, DNP-HSA induces IgE-mediated degranulation in all four cell lines which is inhibitable by anti-CD81 mAb 5D1. 2.4G2/anti-rat IgG F(ab')2 preformed complexes, but not anti-rat IgG F(ab)2 alone, induce degranulation only in cells expressing mFc.gamma.RIII receptors (RBL-2H3 transfectants A10, D10 and H11), a process which is also inhibitable by preincubation with 5D1. This data provides the identification of CD81 as a common inhibitor of both Fc.epsilon.RI and Fc.gamma.RIII.

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TITLE: Calcium-independent negative regulation by CD81 of receptor signaling

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PARENT-CASE:
RELATED APPLICATION This application claims priority to U.S. Provisional Application Ser. No. 60/032,963, filed Dec. 13, 1996, the entire teachings of which are incorporated herein by reference.

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PRIOR-ART-DISCLOSED:

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ART-UNIT: 1646

PRIMARY-EXAMINER: Eyler; Yvonne

ASSISTANT-EXAMINER: Basi; Nirmal S.

ABSTRACT:

Calcium independent CD81 inhibition of IgE-mediated degranulation in mast cells, particularly through the Fc.gamma.RIII and FC.epsilon.RI receptors, is described, as well as methods of inhibiting allergic processes.

2 Claims, 27 Drawing figures

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? s tapa and (antisens? or ribozym? or antibod?)
             317  TAPA
           35212  ANTISENS?
            6071  RIBOZYM?
         1115505  ANTIBOD?
      S1     144  TAPA AND (ANTISENS? OR RIBOZYM? OR ANTIBOD?)
? rd
...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
      S2     108  RD (unique items)
? s s2 and py<2002
Processing
             108  S2
        24988232  PY<2002
      S3     101  S2 AND PY<2002
? s s3 and py>1990
             101  S3
        11291014  PY>1990
      S4      96  S3 AND PY>1990
? t s4/3,ab/all

 4/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12579873   21488786   PMID: 11602340
  Surface markers expressed by multipotent human and mouse neural
progenitor cells include tetraspanins and non-protein epitopes.
  Klassen H; Schwartz M R; Bailey A H; Young M J
  Stem Cell Research, Children's Hospital of Orange County, 455 South Main
Street, Orange, CA 92868, USA. hklassen@choc.org
  Neuroscience letters (Ireland)  Oct 26 2001,  312  (3)  p180-2,
ISSN 0304-3940  Journal Code: 7600130
  Contract/Grant No.: EY 09595; EY; NEI
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Surface molecules play important roles in a wide range of cellular
functions, yet little has been reported regarding the expression of such
markers by neural stem cells. Here, multipotent human neural progenitor
cells (hNPCs) were expanded as a monolayer in the presence of
fibroblast/epidermal growth factor, harvested, labeled with monoclonal
antibodies, and analyzed by flow cytometry. Positive markers included
CD9, CD15, CD81, CD95 (Fas), GD(2) ganglioside, and major
histocompatibility complex class I and beta2 microglobulin, as well as low
levels of the hematopoietic stem cell marker CD34. Of these, mouse NPCs
were positive for CD9, CD15, CD81, and GD(2) ganglioside. The markers
reported here have been implicated in a wide range of cellular functions
including proliferation, migration, differentiation, apoptosis, and immune
recognition.


 4/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12568696   21471950   PMID: 11588022
  The dynamics of hepatitis C virus binding to platelets and 2 mononuclear
cell lines.
  Hamaia S; Li C; Allain J P
  Division of Transfusion Medicine, Department of Haematology, University
of Cambridge, Cambridge, United Kingdom.
  Blood (United States)  Oct 15 2001,  98  (8)  p2293-300,  ISSN
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0006-4971 Journal Code: 7603509
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Hepatitis C virus (HCV) binds to platelets in chronically infected patients where free HCV constitutes only about 5% of total circulating virus. Free HCV preferentially binds to human mononuclear cell lines but free and complexed virus binds equally to platelets. The extent of free HCV binding to human Molt-4 T cells (which express CD81) and to human promonocytic U937 cells or to platelets (which do not express CD81) was similar. The binding of free HCV to the cell lines was saturated at a virus dose of 1 IU HCV RNA per cell but binding to platelets was not saturable. Human anti-HCV IgG, but not anti-CD81, markedly inhibited HCV binding to target cells in a dose-dependent manner. Human **antibodies** to HCV hypervariable region 1 of E2 glycoprotein partially inhibited viral binding to target cells. Recombinant E2 also inhibited viral binding to target cells in a dose-dependent manner, with the efficacy of this decreasing in the rank order of Molt-4 cells more than U937 cells more than platelets. In contrast to HCV, recombinant E2 bound to Molt-4 cells to an extent markedly greater than that apparent with U937 cells or platelets. These results suggest that the binding of HCV to blood cells is mediated by multiple cell surface receptors and that recombinant E2 binding may not be representative of the interaction of the intact virus with target cells.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11305829 21351041 PMID: 11457993

Functional analysis of hepatitis C virus E2 glycoproteins and virus-like particles reveals structural dissimilarities between different forms of E2.

Owsianka A; Clayton R F; Loomis-Price L D; McKeating J A; Patel A H
MRC Virology Unit, Institute of Virology, Church Street, Glasgow G11 5JR, UK.

Journal of general virology (England) Aug **2001**, 82 (Pt 8) p1877-83, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Structure-function analysis of the hepatitis C virus (HCV) envelope glycoproteins, E1 and E2, has been difficult due to the unavailability of HCV virions. Truncated soluble forms of E2 have been used as models to study virus interaction with the putative HCV receptor CD81, but they may not fully mimic E2 structures on the virion. Here, we compared the CD81-binding characteristics of truncated E2 (E2(660)) and full-length (FL) E1E2 complex expressed in mammalian cells, and of HCV virus-like particles (VLPs) generated in insect cells. All three glycoprotein forms interacted with human CD81 in an in vitro binding assay, allowing us to test a panel of well-characterized anti-E2 monoclonal **antibodies** (MAbs) for their ability to inhibit the glycoprotein-CD81 interaction. MAbs specific for E2 amino acid (aa) regions 396-407, 412-423 and 528-535 blocked binding to CD81 of all antigens tested. However, MAbs specific for regions 432-443, 436-443 and 436-447 inhibited the interaction of VLPs, but not of E2(660) or the FL E1E2 complex with CD81, indicating the existence of structural differences amongst the E2 forms. These findings underscore the need to carefully select an appropriate ligand for structure-function analysis.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11290712 21326110 PMID: 11325968

Transmembrane-4 superfamily proteins associate with activated protein kinase C (PKC) and link PKC to specific beta(1) integrins.

Zhang X A; Bontrager A L; Hemler M E

Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, USA.

Journal of biological chemistry (United States) Jul 6 **2001**, 276 (27) p25005-13, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: CA86712; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Translocation of conventional protein kinases C (PKCs) to the plasma membrane leads to their specific association with transmembrane-4 superfamily (TM4SF; tetraspanin) proteins (CD9, CD53, CD81, CD82, and CD151), as demonstrated by reciprocal co-immunoprecipitation and covalent cross-linking experiments. Although formation and maintenance of TM4SF-PKC complexes are not dependent on integrins, TM4SF proteins can act as linker molecules, recruiting PKC into proximity with specific integrins. Previous studies showed that the extracellular large loop of TM4SF proteins determines integrin associations. In contrast, specificity for PKC association probably resides within cytoplasmic tails or the first two transmembrane domains of TM4SF proteins, as seen from studies with chimeric CD9 molecules. Consistent with a TM4SF linker function, only those integrins (alpha(3)beta(1), alpha(6)beta(1), and a chimeric "X3TC5" alpha(3) mutant) that associated strongly with tetraspanins were found in association with PKC. We propose that PKC-TM4SF-integrin structures represent a novel type of signaling complex. The simultaneous binding of TM4SF proteins to the extracellular domains of the integrin alpha(3) subunit and to intracellular PKC helps to explain why the integrin alpha3 extracellular domain is needed for both intracellular PKC recruitment and PKC-dependent phosphorylation of the alpha(3) integrin cytoplasmic tail.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11245137 21272021 PMID: 11376857

Altered sensitivity of CD81-deficient mice to neurobehavioral effects of cocaine.

Michna L; Brenz Verca M S; Widmer D A; Chen S; Lee J; Rogove J; Zhou R; Tsitsikov E; Miescher G C; Dreyer J L; Wagner G C

Department of Toxicology, Rutgers, The State University, New Brunswick, NJ 08854, USA.

Brain research. Molecular brain research (Netherlands) May 20 **2001**, 90 (1) p68-74, ISSN 0169-328X Journal Code: 8908640

Contract/Grant No.: AI 42031; AI; NIAID; RO1 DA11480; DA; NIDA

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

CD81, also known as target of the antiproliferative **antibody**, is known to be expressed in astrocytes and involved in cell adhesion and, recently, we demonstrated its induction exclusively in the accumbens following cocaine. In the present study, the sensitivity of CD81-deficient mice to behavioral effects of cocaine was evaluated. It was found that CD81-deficient mice exhibited altered sensitivity to cocaine as assessed in the place preference conditioning paradigm and locomotor activity. This deficit in place preference conditioning was not accompanied by a deficit in acquisition or retention of water maze behavior. In addition, CD81 knockout mice exhibited higher levels of nucleus accumbens dopamine as compared to their controls. These observations are discussed in the context of the role of CD81 in cocaine-mediated behaviors.

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11199679 21216740 PMID: 11278880
The major CD9 and CD81 molecular partner. Identification and characterization of the complexes.
Charrin S; Le Naour F; Oualid M; Billard M; Faure G; Hanash S M; Boucheix C; Rubinstein E
INSERM U268, Hopital Paul Brousse, 94807 Villejuif Cedex, France.
Journal of biological chemistry (United States) Apr 27 **2001**, 276 (17) p14329-37, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
By associating with specific partner molecules and with each other, the tetraspanins are thought to assemble multimolecular complexes that may be especially relevant with respect to metastasis. We have previously identified a 135-kDa molecule (CD9P-1) as a major molecular partner of CD9 in cancer cell lines. This molecule was identified, after immunoaffinity purification and mass spectrometry analysis, as the protein encoded by the KIAA1436 gene and the human ortholog of a rat protein known as FPRP. Cross-linking experiments detected a complex of the size of CD9 plus CD9P-1, showing that these glycoproteins directly associate with each other, probably in the absence of any other molecule. The use of chimeric CD9/CD82 molecules revealed the role of the second half of CD9, comprising the large extracellular loop and the fourth transmembrane domain. CD9P-1 was also shown to form separate complexes with CD81 and with an unidentified 175-kDa molecule. It also associated with other tetraspanins under conditions maintaining tetraspanin/tetraspanin interactions. The identification of a protein strongly linked to the tetraspanin web and the production of a specific monoclonal **antibody** will help to further characterize the role of this "web" under physiological and pathological conditions.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11178752 21191851 PMID: 11294888
Sequence-specific interaction between the disintegrin domain of mouse ADAM 3 and murine eggs: role of beta1 integrin-associated proteins CD9, CD81, and CD98.
Takahashi Y; Bigler D; Ito Y; White J M
Department of Cell Biology, University of Virginia Health System, School of Medicine, Charlottesville, Virginia 22908, USA.
Molecular biology of the cell (United States) Apr **2001**, 12 (4) p809-20, ISSN 1059-1524 Journal Code: 9201390
Contract/Grant No.: GM-48739; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
ADAM 3 is a sperm surface glycoprotein that has been implicated in sperm-egg adhesion. Because little is known about the adhesive activity of ADAMs, we investigated the interaction of ADAM 3 disintegrin domains, made in bacteria and in insect cells, with murine eggs. Both recombinant proteins inhibited sperm-egg binding and fusion with potencies similar to that which we recently reported for the ADAM 2 disintegrin domain. Alanine scanning mutagenesis revealed a critical importance for the glutamine at position 7 of the disintegrin loop. Fluorescent beads coated with the ADAM 3 disintegrin domain bound to the egg surface. Bead binding was inhibited by an authentic, but not by a scrambled, peptide analog of the disintegrin

loop. Bead binding was also inhibited by the function-blocking anti-alpha6 monoclonal **antibody** (mAb) GoH3, but not by a nonfunction blocking anti-alpha6 mAb, or by mAbs against either the alphav or beta3 integrin subunits. We also present evidence that in addition to the tetraspanin CD9, two other beta1-integrin-associated proteins, the tetraspanin CD81 as well as the single pass transmembrane protein CD98 are expressed on murine eggs. **Antibodies** to CD9 and CD98 inhibited in vitro fertilization and binding of the ADAM 3 disintegrin domain. Our findings are discussed in terms of the involvement of multiple sperm ADAMs and multiple egg beta1 integrin-associated proteins in sperm-egg binding and fusion. We propose that an egg surface "tetraspan web" facilitates fertilization and that it may do so by fostering ADAM-integrin interactions.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11160115 21179883 PMID: 11282207
Immunogenicity of the E1E2 proteins of hepatitis C virus expressed by recombinant adenoviruses.
Seong Y R; Choi S; Lim J S; Lee C H; Lee C K; Im D S
Cell Biology Laboratory, Korea Research Institute of Bioscience and Biotechnology, Yusong PO Box 115, Taejon 305-600, South Korea.
Vaccine (England) Apr 6 **2001**, 19 (20-22) p2955-64, ISSN 0264-410X Journal Code: 8406899
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The E1 and E2 proteins of hepatitis C virus (HCV) are believed to be the viral envelope glycoproteins that are major candidate antigens for HCV vaccine development. We reported previously that the replication-competent recombinant adenovirus encoding core-E1-E2 genes of HCV (Ad/HCV) produces serologically reactive E1 and E2 proteins forming a heterodimer in substantial amounts. Here, we examined immunogenicity of the E1E2 proteins copurified from HeLa cells infected with Ad/HCV virus in mice. Furthermore, we constructed a replication-defective recombinant adenovirus encoding the core-E1-E2 genes of HCV (Ad.CMV.HCV) and examined immunogenicity of the virus in mice. The mice immunized intraperitoneally with the copurified E1E2 proteins induced mainly **antibodies** to E2, but not to E1 by Western blot analysis. The sera of mice immunized with the E1E2 inhibited the binding of E2 protein to the major extracellular loop of human CD81. E2-specific cytotoxic T cells (CTLs), but not **antibodies** to the E1E2 antigens were induced in the mice intramuscularly immunized with Ad.CMV.HCV virus. When immunized with both Ad.CMV.HCV virus and the E1E2, mice elicited E2-specific CTLs and **antibodies** to the E1E2 antigens. The results suggest that immunization of Ad.CMV.HCV virus combined with E2 protein is an effective modality to induce humoral as well as cellular immune response to E2 antigen.

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11157294 21173892 PMID: 11273649
CD81 regulates neuron-induced astrocyte cell-cycle exit.
Kelic S; Levy S; Suarez C; Weinstein D E
Department of Neuroscience, Comprehensive Cancer Center, Albert Einstein College of Medicine, Bronx, New York, 10461, USA.
Molecular and cellular neurosciences (United States) Mar **2001**, 17 (3) p551-60, ISSN 1044-7431 Journal Code: 9100095
Contract/Grant No.: CA-34233; CA; NCI; R01-GM5576001; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed

Astrocytes respond to contact with neurons by cell-cycle arrest and complex process formation. In our effort to discover the molecular mechanisms that underlie this phenomenon we have identified a known tetraspanin, CD81, as a critical component of astrocyte responses to neuronal differentiation signals. Here we show that CD81 is expressed on the surface of the astrocyte and that its expression level can be modulated by contact with neurons. Further, using three separate **antibodies**, 2F7, Eat1, and Eat2, which recognize unique epitopes in the extracellular domains of the CD81 protein, we show that there is a unique domain, recognized by Eat1, that is required for astrocyte cell-cycle withdrawal in response to neurons. This is likely due to conformational changes in the CD81 molecule, as inclusion of 2F7 actually augments neuron-induced astrocyte growth arrest. The critical nature of CD81 in normal astrocyte-neuron biology was confirmed by using mice in which CD81 had been deleted by homologous recombination. Astrocytes null at the CD81 locus were blind to the proliferative arrest encoded on the neuronal cell surface. Taken together, these data strongly suggest that CD81 is a critical regulator of neuron-induced astrocytic differentiation. Copyright 2001 Academic Press.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11126041 21136064 PMID: 11240026

CD81 and microglial activation in vitro: proliferation, phagocytosis and nitric oxide production.

Dijkstra S; Geisert E E; Dijkstra C D; Bar P R; Joosten E A
Department of Experimental Neurology, UMC Utrecht, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands. s.dijkstra@neuro.azu.nl

Journal of neuroimmunology (Netherlands) Mar 1 **2001**, 114 (1-2) p151-9, ISSN 0165-5728 Journal Code: 8109498
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

CD81 (**TAPA**), a member of the tetraspanin family of proteins, is upregulated by astrocytes and microglia after traumatic injury to the rat central nervous system (CNS). To further understand the role of CD81 in the microglial response to injury, we analysed the functional effects of a CD81 **antibody**, AMP1, on cultured rat microglia. We found that AMP1 suppressed microglial proliferation in a dose-dependent manner. Furthermore, AMP1 stimulated myelin phagocytosis, probably by opsonizing the myelin. The phagocytosis of latex beads, as well as the production of nitric oxide, were not significantly influenced by AMP1. These data indicate that CD81 is involved in an important subset of microglial effector functions after CNS injury.

4/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11125622 21135492 PMID: 11241287

Anti-CD81 activates LFA-1 on T cells and promotes T cell-B cell collaboration.

VanCompernolle S E; Levy S; Todd S C
Division of Biology, Program in Molecular Cellular and Developmental Biology, Kansas State University, Manhattan, USA.

European journal of immunology (Germany) Mar **2001**, 31 (3) p823-31, ISSN 0014-2980 Journal Code: 1273201
Contract/Grant No.: 5T32CA9302; CA; NCI; CA34233; CA; NCI
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

CD81 is expressed on human T cells at all stages of development. CD81 is physically associated with CD4 and CD8 and **antibodies** against CD81 generate signals which influence thymocyte adhesion and proliferation. Here we evaluate the function of CD81 on mature T cells. We employ a system in which B cells present superantigen to autologous T cells and find that anti-CD81 promotes T cell-B cell collaboration. Anti-CD81 induces T cell-B cell adhesion of peripheral blood lymphocytes which is partially mediated by LFA-1. CD81 engagement promotes LFA-1-dependent T cell activation, IL-2 production and proliferation. The **antibody** 5A6 was uniquely potent in exerting these effects compared to another **antibody** to CD81 or to **antibodies** that react with other tetraspanins expressed on T cells, anti-CD53 or anti-CD82. CD81-derived signals rapidly induce high-avidity LFA-1 as measured by cell binding to recombinant ICAM-3-coated fluorescent microspheres or by cell adhesion to ICAM-3-coated plastic. 5A6 activation of LFA-1 does not expose the high-affinity conformation epitope recognized by monoclonal **antibody** 24.

4/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11014145 21015389 PMID: 11130883

CD81 nucleotide mutation in hepatocellular carcinoma and lack of CD81 polymorphism in patients at stages of hepatitis C virus infection.

Itakura J; Nagayama K; Enomoto N; Sakamoto N; Tazawa J; Izumi N; Marumo F ; Sato C
Second Department of Internal Medicine, Faculty of Medicine, Tokyo Medical and Dental University, Japan.

Journal of medical virology (United States) Jan **2001**, 63 (1) p22-8, ISSN 0146-6615 Journal Code: 7705876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Mechanisms determining the chronicity or the pattern of clinical course of hepatitis C virus (HCV) infections have not been clarified. Recently, CD81 was reported to bind the E2 protein of HCV and was suggested to function as a cellular receptor for HCV. Accordingly, the hypothesis was examined that CD81 polymorphism, if it exists, might correlate with certain clinical courses of HCV infection. CD81 cDNA sequences were determined from peripheral blood mononuclear cells (PBMCs). Twenty-four Japanese subjects were enrolled initially as follows: patients with chronic hepatitis C without cirrhosis (n = 3), patients with cirrhosis (n = 3), patients with cirrhosis complicated by hepatocellular carcinoma (HCC) (n = 3), patients with persistent HCV viremia without ALT elevation (n = 3), those with positive anti-HCV **antibodies** without evidence of HCV viremia (n = 3), and healthy volunteers (n = 9). In all PBMCs samples analyzed, no polymorphism was found in the CD81 cDNA sequence. The sequence was different, however, from the one reported previously at three nucleotide positions: a transversion to thymine instead of cytosine at nt 1130, a deletion at nt 1206, and a guanine insertion at nt 71. Subsequently, CD81 cDNA sequences from PBMCs and HCC tissue were compared among the other 6 patients with chronic hepatitis C bearing HCC. A comparative study of the CD81 sequences from HCC and PBMCs revealed that various nucleotide mutations existed only in the HCC samples in 3 out of 6 patients. Several mutations in the 3' non-coding region of CD81 cDNA were observed exclusively in HCC tissue suggesting its possible role in hepatocarcinogenesis. Because of the absence of polymorphisms, however, CD81 is unlikely to affect the progression of chronic hepatitis C in terms of chronicity, hepatitis activity, or disease stage.

4/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10968151 20519721 PMID: 11064366
Up-regulation of CD81 (target of the antiproliferative **antibody**; **TAPA**) by reactive microglia and astrocytes after spinal cord injury in the rat.
Dijkstra S; Geisert EE J R; Gispen W H; Bar P R; Joosten E A
Department of Experimental Neurology, RMI for Neurosciences, University Medical Centre, 3508 GA Utrecht, The Netherlands. s.dijkstra@neuro.azu.nl
Journal of comparative neurology (UNITED STATES) Dec 11 **2000**, 428 (2) p266-77, ISSN 0021-9967 Journal Code: 0406041
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We examined the expression of CD81 (also known as **TAPA**, or target of the antiproliferative **antibody**) after traumatic spinal cord injury in the rat. CD81, a member of the tetraspanin family of proteins, is thought to be involved in reactive gliosis. This is based on the antiproliferative and antiadhesive effects of **antibodies** against CD81 on cultured astrocytes, as well as its up-regulation after penetrating brain injury. CD81 expression following dorsal hemisection of the spinal cord was determined immunohistochemically at time points ranging from 1 day to 2 months postlesion (p.l.). In the unlesioned cord a low background level of CD81 was observed, with the exception of the ependyma of the central canal and the pia mater, which were strongly CD81-positive. One day p.l., CD81 was diffusely up-regulated in the spinal cord parenchyma surrounding the lesion site. From 3 days onward, intensely CD81-positive round cells entered the lesion site, completely filling it by 7 days p.l. Staining with the microglial markers OX-42 and Iba1 revealed that these cells were reactive microglia/macrophages. At this time, no significant CD81 expression by GFAP-positive reactive astrocytes was noted. From the second week onward, CD81 was gradually down-regulated; i.e., its spatial distribution became more restricted. The CD81-positive microglia/macrophages disappeared from the lesion site, leaving behind large cavities. After 2 months, astrocytes that formed the wall of these cavities were strongly CD81-positive. In addition, CD81 was present on reactive astrocytes in the dorsal funiculus distal from the lesion in degenerated white matter tracts. In conclusion, the spatiotemporal expression pattern of CD81 by reactive microglia and astrocytes indicates that CD81 is involved in the glial response to spinal cord injury.

4/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10961997 20540025 PMID: 11086118
Construction and characterization of chimeric hepatitis C virus E2 glycoproteins: analysis of regions critical for glycoprotein aggregation and CD81 binding.
Patel A H; Wood J; Penin F; Dubuisson J; McKeating J A
MRC Virology Unit, Institute of Virology, Church Street, Glasgow G11 5JR, UK. a.patel@vir.gla.ac.uk
Journal of general virology (ENGLAND) Dec **2000**, 81 Pt 12 p2873-83, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We compared the ability of two closely related truncated E2 glycoproteins (E2(660)) derived from hepatitis C virus (HCV) genotype 1a strains Glasgow

(Gla) and H77c to bind a panel of conformation-dependent monoclonal **antibodies** (MAbs) and CD81. In contrast to H77c, Gla E2(660) formed disulfide-linked high molecular mass aggregates and failed to react with conformation-dependent MAbs and CD81. To delineate amino acid (aa) regions associated with protein aggregation and CD81 binding, several Gla-H77c E2(660) chimeric glycoproteins were constructed. Chimeras C1, C2 and C6, carrying aa 525-660 of Gla E2(660), produced disulfide-linked aggregates and failed to bind CD81 and conformation-dependent MAbs, suggesting that amino acids within this region are responsible for protein misfolding. The presence of Gla hypervariable region 1 (aa 384-406) on H77 E2(660), chimera C4, had no effect on protein folding or CD81 binding. Chimeras C3 and C5, carrying aa 384-524 or 407-524 of Gla E2(660), respectively, were recognized by conformation-dependent MAbs and yet failed to bind CD81, suggesting that amino acids in region 407-524 are important in modulating CD81 interaction without affecting antigen folding. Comparison of Gla and H77c E2(660) aa sequences with those of genotype 1a and divergent genotypes identified a number of variant amino acids, including two putative N-linked glycosylation sites at positions 476 and 532. However, introduction of G476N-G478S and/or D532N in Gla E2(660) had no effect on antigenicity or aggregation.

4/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10961914 20534982 PMID: 11080483
Hepatitis C virus envelope protein E2 binds to CD81 of tamarins.
Allander T; Forns X; Emerson S U; Purcell R H; Bukh J
Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-0740, USA.
Virology (UNITED STATES) Nov 25 **2000**, 277 (2) p358-67, ISSN 0042-6822 Journal Code: 0110674
Contract/Grant No.: CO-56000; CO; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Since recombinant envelope glycoprotein E2 of hepatitis C virus (HCV) binds to CD81 on human and chimpanzee cells, it has been suggested that CD81 may be a receptor for HCV. Humans and chimpanzees are the only species known to be susceptible to HCV infection. E2 has been reported not to bind to CD81 of the African green monkey, mouse, or rat, suggesting that binding of HCV to CD81 is species specific and may determine susceptibility to infection with HCV. We investigated the interaction between E2 of HCV and CD81 of tamarins, a group of small New World monkeys frequently used for the study of human viruses. Tamarins are not susceptible to HCV infection. Nonetheless, we found that three different forms of HCV E2 (intracellular, secreted, and cell surface-displayed) bound more efficiently to recombinant tamarin CD81 than to human CD81, as determined by ELISA and immunofluorescence. The affinity of the interaction was approximately 10-fold higher for tamarin than for human CD81. Binding of E2 to CD81 on cultured or primary tamarin cells was demonstrated by flow cytometry. In contrast to previous reports, there was also a low-affinity interaction between E2 and African green monkey CD81. Thus, the HCV E2 interaction with CD81 is not limited to humans and chimpanzees and does not predict susceptibility to HCV infection.

4/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10938445 20499063 PMID: 11044085
Human monoclonal **antibodies** that inhibit binding of hepatitis C

virus E2 protein to CD81 and recognize conserved conformational epitopes.
Hadlock K G; Lanford R E; Perkins S; Rowe J; Yang Q; Levy S; Pileri P; Abrignani S; Foung S K
Departments of Pathology, Stanford University, Stanford, CA 94304, USA.
Journal of virology (UNITED STATES) Nov **2000**, 74 (22) p10407-16, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: AI40035; AI; NIAID; DA-06596; DA; NIDA; HL-33811; HL; NHLBI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The intrinsic variability of hepatitis C virus (HCV) envelope proteins E1 and E2 complicates the identification of protective **antibodies**. In an attempt to identify **antibodies** to E2 proteins from divergent HCV isolates, we produced HCV E2 recombinant proteins from individuals infected with HCV genotypes 1a, 1b, 2a, and 2b. These proteins were then used to characterize 10 human monoclonal **antibodies** (HMAbs) produced from peripheral B cells isolated from an individual infected with HCV genotype 1b. Nine of the **antibodies** recognize conformational epitopes within HCV E2. Six HMAbs identify epitopes shared among HCV genotypes 1a, 1b, 2a, and 2b. Six, including five broadly reactive HMAbs, could inhibit binding of HCV E2 of genotypes 1a, 1b, 2a, and 2b to human CD81 when E2 and the **antibody** were simultaneously exposed to CD81. Surprisingly, all of the **antibodies** that inhibited the binding of E2 to CD81 retained the ability to recognize preformed CD81-E2 complexes generated with some of the same recombinant E2 proteins. Two **antibodies** that did not recognize preformed complexes of HCV 1a E2 and CD81 also inhibited binding of HCV 1a virions to CD81. Thus, HCV-infected individuals can produce **antibodies** that recognize conserved conformational epitopes and inhibit the binding of HCV to CD81. The inhibition is mediated via **antibody** binding to epitopes outside of the CD81 binding site in E2, possibly by preventing conformational changes in E2 that are required for CD81 binding.

4/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10912987 20451111 PMID: 10993933
Recombinant human monoclonal **antibodies** against different conformational epitopes of the E2 envelope glycoprotein of hepatitis C virus that inhibit its interaction with CD81.
Allander T; Drakenberg K; Beyene A; Rosa D; Abrignani S; Houghton M; Widell A; Grillner L; Persson M A
Karolinska Institute, Department of Medicine and Department of Laboratory Medicine, Center for Molecular Medicine (L8:01), Karolinska Hospital, S-171 76 Stockholm, Sweden.
Journal of general virology (ENGLAND) Oct **2000**, 81 Pt 10 p2451-9, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **antibody** response to the envelope proteins of hepatitis C virus (HCV) may play an important role in controlling the infection. To allow molecular analyses of protective **antibodies** , we isolated human monoclonal **antibodies** to the E2 envelope glycoprotein of HCV from a combinatorial Fab library established from bone marrow of a chronically HCV-infected patient. Anti-E2 reactive clones were selected using recombinant E2 protein. The bone marrow donor carried HCV genotype 2b, and E2 used for selection was of genotype 1a. The **antibody** clones were expressed as Fab fragments in E. coli, and as Fab fragments and IgG1 in CHO cells. Seven different **antibody** clones were characterized, and shown

to have high affinity for E2, genotype 1a. Three clones also had high affinity for E2 of genotype 1b. They all bind to conformation-dependent epitopes. Five clones compete for the same or overlapping binding sites, while two bind to one or two other epitopes of E2. Four clones corresponding to the different epitopes were tested as purified IgG1 for blocking the CD81-E2 interaction in vitro; all four were positive at 0.3-0.5 microg/ml. Thus, the present results suggest the existence of at least two conserved epitopes in E2 that mediate inhibition of the E2-CD81 interaction, of which one appeared immunodominant in this donor.

4/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10884261 20431899 PMID: 10974114
Mosaic plasmids and mosaic replicons: evolutionary lessons from the analysis of genetic diversity in IncFII-related replicons.
Osborn A M; da Silva Tatley F M; Steyn L M; Pickup R W; Saunders J R
School of Biological Sciences, Life Science Building, The University of Liverpool, PO Box 147, Liverpool L69 7ZB, UK.
Microbiology (Reading, England) (ENGLAND) Sep **2000**, 146 (Pt 9) p2267-75, ISSN 1350-0872 Journal Code: 9430468
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The alpha replicons of the multi-replicon plasmids pGSH500 and pLV1402 have been characterized by DNA sequence analysis. Analysis of the DNA sequence of a 3672 bp HIN:dIII fragment from pFDT100, which contains the pGSH500 alpha replicon, revealed similarity to a number of replicons belonging to, or related to, those of the IncFII family. The replicon region contains copA, **tapA**, repA and oriR, and replication initiation and termination sites are related to those from the IncFII replicon of R1. A copB gene was found to lie upstream of the HIN:dIII site in the parental plasmid pGSH500. Downstream of oriR, a 707 bp region shows 72.6% identity to a region of the Escherichia coli chromosome at 43.3', suggesting this region of pGSH500 may have been incorporated into the plasmid during a past chromosomal recombination event. Oligonucleotide primers homologous to consensus regions in the copB and repA genes, and the oriR regions from a number of IncFII-related replicons were used to amplify replication regions from pLV1402. Analysis of the amplified regions has shown the presence of copB, copA, **tapA** and repA genes. Phylogenetic analysis of Rep protein sequences from the RepFIIA family of **antisense**-control-regulated replicons revealed the presence of three distinct subgroups of Rep proteins. Comparative analysis of DNA and protein sequences from members of the RepFIIA family provides evidence supporting the roles of both non-selective divergence in co-integrate (multi-replicon) plasmids and Chi-mediated-recombination in replicon evolution, and in particular, that such processes may have been widespread in the evolution of the RepFIIA family.

4/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10847353 20396576 PMID: 10936090
Characterization of modified hepatitis C virus E2 proteins expressed on the cell surface.
Forns X; Allander T; Rohwer-Nutter P; Bukh J
Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA. XFORNS@clinic.ub.es
Virology (UNITED STATES) Aug 15 **2000**, 274 (1) p75-85, ISSN 0042-6822 Journal Code: 0110674

Contract/Grant No.: CO-56000; CO; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The envelope proteins of hepatitis C virus (HCV) are the likely targets of neutralizing **antibodies** and their molecular and functional characterization is relevant for vaccine development. We previously showed that surface-expressed E2 is a better immunogen than intracellular E2 and, therefore, we were interested in exploring more efficient ways to present E2 protein on the cell surface. We found that E2 targeted to the cell surface by replacement of its transmembrane domain did not bring E1 to the surface although E1 could be expressed independently on the cell surface if its transmembrane domain was similarly replaced. FACS analysis suggested that E2 expressed on the cell surface acquired its native conformation more efficiently when truncated at aa 661 than when truncated at aa 715. The shorter form of truncated E2 better retained the ability to bind the second extracellular loop (EC2) of CD81, the putative HCV receptor. Interestingly, deletion of the hypervariable region 1 (HVR1) did not perceptibly alter E2 structure; cell-surface forms of E2 lacking the HVR1 remained reactive with conformation-sensitive MAbs and were able to bind recombinant EC2 of CD81.

4/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10823838 20363096 PMID: 10907850

Sequence-based structural features between Kvlqt1 and Tapa1 on mouse chromosome 7F4/F5 corresponding to the Beckwith-Wiedemann syndrome region on human 11p15.5: long-stretches of unusually well conserved intronic sequences of kvlqt1 between mouse and human.

Yatsuki H; Watanabe H; Hattori M; Joh K; Soejima H; Komoda H; Xin Z; Zhu X; Higashimoto K; Nishimura M; Kuratomi S; Sasaki H; Sakaki Y; Mukai T
Department of Biochemistry, Saga Medical School, Saga, Japan.

DNA research : an international journal for rapid publication of reports on genes and genomes (JAPAN) Jun 30 **2000**, 7 (3) p195-206, ISSN 1340-2838 Journal Code: 9423827
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Mouse chromosome 7F4/F5 is a syntenic locus of human 11p15.5 in which many imprinted genes are clustered. Transmission of aberrant human 11p15.5 or duplicated 11p causes Beckwith-Wiedemann syndrome (BWS) depending on which parent the chromosome is derived from. To analyze a syntenic mouse locus corresponding to human 11p15.5, mouse BAC contigs were constructed between Nap2 and Tapa1, in which 390 kb was sequenced between Kvlqt1 and Tapa1. An unexpected finding was that of highly conserved intronic sequences of Kvlqt1 between mouse and human, and their homologies came up to at least 160 kb because the length of this gene extended to 350 kb, suggesting the possibility of some functional constraint due to transcriptional and/or post-transcriptional regulation of this region. Many expressed sequence tags (ESTs) were mapped on this locus. Three genes, Lit1 (Kvlqt1-AS), Mtr1 and Tssc4, were identified and characterized. Lit1 is an **antisense** -transcript of Kvlqt1 and paternally expressed and maternally methylated throughout the developmental stage. The position where Lit1 exists corresponded to a highly conserved region between mouse and human. This transcript extends at least 60 kb from downstream to upstream of exon 10 in Kvlqt1. Tssc4 and Mtr1 carried putative open reading frames but neither was imprinted. Further characterization of this locus based on the sequence comparison between mouse and human will contribute valuable information towards resolving the mechanism of the occurrence of BWS and the associated childhood tumor.

4/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10811107 20351724 PMID: 10891408
Hepatitis C virus glycoprotein E2 binding to CD81: the role of E1E2 cleavage and protein glycosylation in bioactivity.
Chan-Fook C; Jiang W R; Clarke B E; Zitzmann N; Maidens C; McKeating J A; Jones I M
NERC Institute of Virology and Environmental Microbiology, Mansfield Road, Oxford, OX1 3SR.
Virology (UNITED STATES) Jul 20 **2000**, 273 (1) p60-6, ISSN 0042-6822 Journal Code: 0110674
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hepatitis C virus glycoproteins E1 and 2 have been expressed using recombinant baculoviruses following fusion to the carrier protein glutathione S-transferase (GST). Proteins were expressed singly and as an E1E2 polyprotein with and without an N-terminal affinity tag. Expression of the E1E2 polyprotein, even when preceded by GST, led to processing in insect cells and detection of an E1E2 complex that could be specifically purified by glutathione affinity chromatography. Baculovirus expressed E2 and a purified GST-E1E2 protein bound to the second extracellular loop of CD81 (EC2), a reported ligand for the molecule, but not to a truncated derivative of CD81 consisting of only the central domain of the loop. Purified GST-E2, however, failed to bind to CD81 suggesting a requirement for a free E2 amino terminus for biological activity. The binding to CD81 by baculovirus expressed E2 protein was comparable to that observed for E2 derived from mammalian cells when detected by a monoclonal **antibody** sensitive to protein conformation. Furthermore, E2 protein expressed in insect cells in the presence of N-butyldeoxynojirimycin, an inhibitor of terminal glucose residue processing, formed complexes with E1 and bound to CD81-EC2 similarly to untreated protein. Together these data suggest that although hyperglucosylation of E2 does not have a major effect on bioactivity, polyprotein processing to reveal the free amino terminus is required. Copyright 2000 Academic Press.

4/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806570 20347351 PMID: 10888628
Evaluation of hepatitis C virus glycoprotein E2 for vaccine design: an endoplasmic reticulum-retained recombinant protein is superior to secreted recombinant protein and DNA-based vaccine candidates.
Heile J M; Fong Y L; Rosa D; Berger K; Saletti G; Campagnoli S; Bensi G; Capo S; Coates S; Crawford K; Dong C; Wininger M; Baker G; Cousens L; Chien D; Ng P; Archangel P; Grandi G; Houghton M; Abrignani S
IRIS Research Center, Chiron, 53100 Siena, Italy.
Journal of virology (UNITED STATES) Aug **2000**, 74 (15) p6885-92
, ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) is the leading causative agent of blood-borne chronic hepatitis and is the target of intensive vaccine research. The virus genome encodes a number of structural and nonstructural antigens which could be used in a subunit vaccine. The HCV envelope glycoprotein E2 has recently been shown to bind CD81 on human cells and therefore is a prime candidate for inclusion in any such vaccine. The experiments

presented here assessed the optimal form of HCV E2 antigen from the perspective of **antibody** generation. The quality of recombinant E2 protein was evaluated by both the capacity to bind its putative receptor CD81 on human cells and the ability to elicit **antibodies** that inhibited this binding (NOB **antibodies**). We show that truncated E2 proteins expressed in mammalian cells bind with high efficiency to human cells and elicit NOB **antibodies** in guinea pigs only when purified from the core-glycosylated intracellular fraction, whereas the complex-glycosylated secreted fraction does not bind and elicits no NOB **antibodies**. We also show that carbohydrate moieties are not necessary for E2 binding to human cells and that only the monomeric nonaggregated fraction can bind to CD81. Moreover, comparing recombinant intracellular E2 protein to several E2-encoding DNA vaccines in mice, we found that protein immunization is superior to DNA in both the quantity and quality of the **antibody** response elicited. Together, our data suggest that to elicit **antibodies** aimed at blocking HCV binding to CD81 on human cells, the antigen of choice is a mammalian cell-expressed, monomeric E2 protein purified from the intracellular fraction.

4/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10754983 20304866 PMID: 10844555
Tetraspanins are localized at motility-related structures and involved in normal human keratinocyte wound healing migration.
Penas P F; Garcia-Diez A; Sanchez-Madrid F; Yanez-Mo M
Departments of Dermatology and Immunology, Hospital Universitario de La Princesa, Universidad Autonoma de Madrid, Spain. pablofp@hup.es
Journal of investigative dermatology (UNITED STATES) Jun **2000**, 114 (6) p1126-35, ISSN 0022-202X Journal Code: 0426720
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have described previously that beta1 integrins, which mediate keratinocyte cell adhesion and migration, are in ligand-occupied conformation at the basal surface but not at the lateral and apical surfaces of keratinocytes. This led us to study the cellular localization and function of tetraspanin molecules, which have been postulated to modulate integrin activity. We found that CD9 and CD81 are highly expressed by keratinocytes clearly delineating filopodia at lateral and apical surfaces. CD63 and CD151 are largely expressed in the intracellular compartment, although some membrane expression is observed. We found accumulation of CD9, CD81, and CD151 together with alpha3 and beta1 integrins at intercellular junctions. In low calcium medium, this intercellular space is crossed by a zipper of filopodia enriched in alpha3beta1 and tetraspanin proteins. Interestingly, the expression of CD9, CD81, and beta1 and alpha3 integrins was detected in the footprints and rippings of motile keratinocytes, suggesting their role in both adhesion to extracellular matrix and keratinocyte motility. beta1 integrins were only partially activated in the rips, whereas cytoskeleton-linking proteins such as talin were completely absent. On the other hand, antitetraspanin **antibodies** did not stain focal adhesions, which contain talin. The involvement of tetraspanins in keratinocyte motility was assessed in a wound healing migration assay. Inhibition of cell migration was observed with **antibodies** to CD9, CD81, beta1, and alpha3, and, to a lesser extent, to CD151. Together these results indicate that tetraspanin-integrin complexes might be involved in transient adhesion and integrin recycling during keratinocyte migration, as well as in intercellular recognition.

4/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10740031 20267869 PMID: 10806098
Transmembrane-4-superfamily proteins CD151 and CD81 associate with alpha 3 beta 1 integrin, and selectively contribute to alpha 3 beta 1-dependent neurite outgrowth.
Stipp C S; Hemler M E
Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute and Department of Pathology, Harvard Medical School, Boston, MA 02115, USA.
Journal of cell science (ENGLAND) Jun **2000**, 113 (Pt 11) p1871-82, ISSN 0021-9533 Journal Code: 0052457
Contract/Grant No.: GM38903; GM; NIGMS; NS10344; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Proteins in the transmembrane-4-superfamily (TM4SF) form many different complexes with proteins in the integrin family, but the functional utility of these complexes has not yet been demonstrated. Here we show that TM4SF proteins CD151, CD81, and CD63 co-distribute with alpha3beta1 integrin on neurites and growth cones of human NT2N cells. Also, stable CD151-alpha3beta1 and CD81-alpha3beta1 complexes were recovered in NT2N detergent lysates. Total NT2N neurite outgrowth on laminin-5 (a ligand for alpha3beta1 integrin) was strongly inhibited by anti-CD151 and -CD81 **antibodies** either together (approximately 85% inhibition) or alone (approximately 45% inhibition). Notably, these **antibodies** had no inhibitory effect on NT2N neurites formed on laminin-1 or fibronectin, when alpha3beta1integrin was not engaged. Neurite number, length, and rate of extension were all affected by anti-TM4SF **antibodies**. In summary: (1) these substrate-dependent inhibition results strongly suggest that CD151 and CD81 associations with alpha3beta1 are functionally relevant, (2) TM4SF proteins CD151 and CD81 make a strong positive contribution toward neurite number, length, and rate of outgrowth, and (3) NT2N cells, a well-established model of immature central nervous system neurons, can be a powerful system for studies of integrin function in neurite outgrowth and growth cone motility.

4/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10708233 20229324 PMID: 10768837
Differential expression of murine CD81 highlighted by new anti-mouse CD81 monoclonal **antibodies**.
Maecker H T; Todd S C; Kim E C; Levy S
Department of Medicine, Stanford University Medical Center, CA 94305, USA.
Hybridoma (UNITED STATES) Feb **2000**, 19 (1) p15-22, ISSN 0272-457X Journal Code: 8202424
Contract/Grant No.: 5T32CA9302; CA; NCI; CA34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We describe the use of a soluble CD81-Fc fusion protein to screen for novel monoclonal **antibody** (MAb) reactive with the extracellular loops of murine CD81 (**TAPA** -1). Two such MAbs, Eat1 and Eat2 (for Extracellular Anti-TAPA1), were used to assess the expression and function of CD81 on murine lymphocytes. Although CD81 is expressed uniformly on all human lymphocytes, murine CD81 was found to be expressed at much higher levels on resting B cells than on resting T cells. This was particularly evident when staining with the new MAbs, Eat1 and Eat2. The molecule is also functionally active on B cells, as Eat1 and Eat2 induce homotypic adhesion of B lymphocytes. Stimulated B cells undergo early apoptotic events in the presence of Eat2, as shown by binding of Annexin

V-fluorescein isothiocyanate (FITC). Polyclonal activation of murine T cells also induces higher level CD81 expression, and many immortalized murine T-cell lines express high levels of the protein. In contrast to human CD81, which is expressed equally on all thymocytes, murine CD81 is induced during thymic development, being expressed at high levels on CD4+CD8+ thymocytes, in contrast to other subsets of thymocytes. Finally, murine dendritic cells, splenic macrophages, and non-killer (NK) cells all express high levels of CD81. We conclude that CD81 is differentially expressed in the murine immune system, and is involved in regulating the adhesion and activation of murine B cells.

4/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10687795 20240068 PMID: 10775621
Structure-function analysis of hepatitis C virus envelope-CD81 binding.
Petracca R; Falugi F; Galli G; Norais N; Rosa D; Campagnoli S; Burgio V; Di Stasio E; Giardina B; Houghton M; Abrignani S; Grandi G
Chiron Research Centre, 53100 Siena, Italy.
Journal of virology (UNITED STATES) May **2000**, 74 (10) p4824-30
, ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) is a major human pathogen causing chronic liver disease. We have recently found that the large extracellular loop (LEL) of human CD81 binds HCV. This finding prompted us to assess the structure-function features of HCV-CD81 interaction by using recombinant E2 protein and a recombinant soluble form of CD81 LEL. We have found that HCV-E2 binds CD81 LEL with a K(d) of 1.8 nM; CD81 can mediate attachment of E2 on hepatocytes; engagement of CD81 mediates internalization of only 30% of CD81 molecules even after 12 h; and the four cysteines of CD81 LEL form two disulfide bridges, the integrity of which is necessary for CD81-HCV interaction. Altogether our data suggest that neutralizing **antibodies** aimed at interfering with HCV binding to human cells should have an affinity higher than 10(-9) M, that HCV binding to hepatocytes may not entirely depend on CD81, that CD81 is an attachment receptor with poor capacity to mediate virus entry, and that reducing environments do not favor CD81-HCV interaction. These studies provide a better understanding of the CD81-HCV interaction and should thus help to elucidate the viral life cycle and to develop new strategies aimed at interfering with HCV binding to human cells.

4/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10685891 20224626 PMID: 10761560
The rheumatoid factor response in the etiology of mixed cryoglobulins associated with hepatitis C virus infection.
Sasso E H
Department of Medicine, University of Washington, Seattle 98105, USA.
Annales de medecine interne (FRANCE) Feb **2000**, 151 (1) p30-40,
ISSN 0003-410X Journal Code: 0171744
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Studies of mixed cryoglobulins (MC) from patients infected with hepatitis C virus (HCV) show that the principal constituents in cryoprecipitate are IgM rheumatoid factors (RF), polyclonal IgG anti-HCV **antibodies**, and HCV RNA. The HCV-induced RF response is biased to produce IgM RF encoded by

a restricted set of Ig V genes, predominantly the VH/VL gene pair 51p1/kv325. The propensity of such IgM RF to cryoprecipitate is likely a coincidental property of their V region sequences, but the clinical effect of this bias is increased by the persistence of circulating HCV-IgG immune complexes. These complexes might induce production of cryoprecipitable IgM RF and furnish multi-molecular structures that favor binding by cryoprecipitable IgM RF. The V gene sequences of HCV-induced IgM RF have features seen in other RF responses, suggesting a common immunological mechanism that is independent of HCV. B cell proliferation is probably enhanced by HCV-specific properties, however, including the ability of HCV proteins to bind to CD81 on the B cell surface, and to influence intracellular regulatory functions following viral entry into B cells. The V gene bias in HCV-induced RF is most apparent among the B cells in monoclonal expansions responsible for type II cryoglobulins, but it might originate early the polyclonal RF response, before MC are detectable. Monoclonal B cell expansions and lymphomatoid bone marrow infiltrates in HCV+ patients predominantly involve CD5-negative IgM RF B cells. Non-RF B cells can also be expanded, including producers of IgG1 and IgG3 that are likely anti-HCV **antibodies** . The initial site of B cell clonal expansion may be in the liver, where lymphoid aggregates are abundant and RF are produced. Sorting out how MC formation is influenced by properties that are inherent to the RF response, or specific to HCV infection, will be a challenge to future HCV research.

4/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10663011 20193804 PMID: 10729140
Identification of amino acid residues in CD81 critical for interaction with hepatitis C virus envelope glycoprotein E2.
Higginbottom A; Quinn E R; Kuo C C; Flint M; Wilson L H; Bianchi E; Nicosia A; Monk P N; McKeating J A; Levy S
Department of Molecular Biology, University of Sheffield, Sheffield S10 2UH, United Kingdom.
Journal of virology (UNITED STATES) Apr **2000**, 74 (8) p3642-9, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: CA-34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human CD81 has been previously identified as the putative receptor for the hepatitis C virus envelope glycoprotein E2. The large extracellular loop (LEL) of human CD81 differs in four amino acid residues from that of the African green monkey (AGM), which does not bind E2. We mutated each of the four positions in human CD81 to the corresponding AGM residues and expressed them as soluble fusion LEL proteins in bacteria or as complete membrane proteins in mammalian cells. We found human amino acid 186 to be critical for the interaction with the viral envelope glycoprotein. This residue was also important for binding of certain anti-CD81 monoclonal **antibodies**. Mutating residues 188 and 196 did not affect E2 or **antibody** binding. Interestingly, mutation of residue 163 increased both E2 and **antibody** binding, suggesting that this amino acid contributes to the tertiary structure of CD81 and its ligand-binding ability. These observations have implications for the design of soluble high-affinity molecules that could target the CD81-E2 interaction site(s).

4/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10625207 20158364 PMID: 10695817
A new sensitive and specific combination of CD81/CD56/CD45 monoclonal

antibodies for detecting circulating neuroblastoma cells in peripheral blood using flow cytometry.

Nagai J; Ishida Y; Koga N; Tanaka Y; Ohnuma K; Toyoda Y; Katoh A; Hayabuchi Y; Kigasawa H

Division of Laboratory, Kanagawa Children's Medical Center, Yokohama, Japan.

Journal of pediatric hematology/oncology : official journal of the American Society of Pediatric Hematology/Oncology (UNITED STATES) Jan-Feb **2000**, 22 (1) p20-6, ISSN 1077-4114 Journal Code: 9505928

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

PURPOSE: Intensive chemoradiotherapy followed by peripheral blood stem cell transplantation has been introduced to treat children with advanced neuroblastoma (NBL). Detection of NBL cells in peripheral blood (PB) is important to prevent reinfusion of NBL cells. Several immunologic methods have been proposed for detecting NBL cells in hematologic samples. The development of a sensitive and specific combination of monoclonal **antibodies** (MoAbs) for detecting small numbers of NBL cells in PB using flow cytometry remains an important challenge. METHODS: Twenty-one clinical samples from NBL tissues or smears containing NBL cells were examined for reactivity against CD81, CD56, and CD9 using an immunocytochemical technique. The expressions of CD81, CD56, CD9, and antihuman disialoganglioside GD2 MoAb (GD2) in five NBL cell lines were assayed by flow cytometry. For the evaluation of sensitivity, five NBL cell lines were added to normal PB and the detection level of the combination of CD81/CD56/CD45 MoAbs was compared with that of CD9/CD56/CD45 MoAbs (reported previously). One hundred thirty-three normal PB samples were examined to determine the sensitivity and specificity of this method. RESULTS: All NBL cell lines showed strong positivity with CD81 and CD56 MoAb. However, CD9 MoAb was weakly positive against the five NBL cell lines. GD2 MoAb reacted strongly with four NBL cell lines, although almost the entire cell population of the SK-N-SH NBL line failed to bind the GD2 MoAb. In vitro experiments using NBL cell lines demonstrated that tumor cells added to normal PB cells could be detected by flow cytometry using CD81/CD56/CD45 MoAbs even at a concentration of 0.005%. Through comparative studies, the combination of CD81/CD56/CD45 MoAbs was found to be more sensitive and specific than that of CD9/CD56/CD45 MoAbs for detecting small numbers of NBL cells using the above cell lines. CONCLUSIONS: Triple-color flow cytometric analysis using CD81/CD56/CD45 MoAbs is useful for detecting NBL cells in PB. Further studies testing this approach using samples of PB with NBL contamination are needed to test this approach in patients.

4/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10554330 20073537 PMID: 10605604

The role of complement in B cell activation and tolerance.

Carroll M C

Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

Advances in immunology (UNITED STATES) **2000**, 74 p61-88, ISSN 0065-2776 Journal Code: 0370425

Document type: Journal Article; Review; Review, Academic

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

It is becoming well accepted that innate immunity serves as a natural adjuvant in enhancing and directing the adaptive immune response. In this review, I have discussed how the complement system, a major mediator of innate immunity, links the two systems. The recent availability of knockout mice bearing selective deficiencies in the critical complement proteins and

receptors has allowed formal demonstration of the importance of complement in enhancement of humoral immunity. Characterization of the mice has also uncovered mechanisms for maintaining survival of activated B cells within the lymphoid compartment. For example, co-ligation of the CD21/CD19/ **Tapa** -1 receptor with the BCR not only reduces the threshold for B cell follicular survival but provides a unique signal for survival in the germinal centers. In addition complement receptors are critical for localization of antigen and C3d ligand to FDCs for maintenance of long-term B cell memory. A surprise that has come from analysis of the deficient mice is that complement is also important in negative selection of B lymphocytes. This observation provides new insight to a long-standing enigma that the major predisposing factor in lupus is deficiency in complement C1q or C4. The seeming contradiction of dual role for complement in both B cell activation and tolerance is reconciled by the hypothesis that natural IgM provides a mechanism to selectively identify self-antigens that are highly conserved and cross-react with microbial ones such as DNA and nuclear proteins. Thus, the importance of complement in tolerance to self-antigens is restricted to those self-antigens that are evolutionary conserved, and they are identified by natural **antibody**. The future should hold further surprises as to the intricate interactions between the complement system and acquired immunity.

4/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10553572 20091325 PMID: 10623732
Functional characterization of intracellular and secreted forms of a truncated hepatitis C virus E2 glycoprotein.
Flint M; Dubuisson J; Maidens C; Harrop R; Guile G R; Borrow P; McKeating J A
School of Animal and Microbial Sciences, University of Reading, Whiteknights, Reading RG6 6AJ, United Kingdom.
Journal of virology (UNITED STATES) Jan **2000**, 74 (2) p702-9, ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The E2 protein of hepatitis C virus (HCV) is believed to be a virion surface glycoprotein that is a candidate for inclusion in an antiviral vaccine. A truncated soluble version of E2 has recently been shown to interact with CD81, suggesting that this protein may be a component of the receptor for HCV. When expressed in eukaryotic cells, a significant proportion of E2 forms misfolded aggregates. To analyze the specificity of interaction between E2 and CD81, the aggregated and monomeric forms of a truncated E2 glycoprotein (E2(661)) were separated by high-pressure liquid chromatography and analyzed for CD81 binding. Nonaggregated forms of E2 preferentially bound CD81 and a number of conformation-dependent monoclonal **antibodies** (MAbs). Furthermore, intracellular forms of E2(661) were found to bind CD81 with greater affinity than the extracellular forms. Intracellular and secreted forms of E2(661) were also found to differ in reactivity with MAbs and human sera, consistent with differences in antigenicity. Together, these data indicate that proper folding of E2 is important for its interaction with CD81 and that modifications of glycans can modulate this interaction. Identification of the biologically active forms of E2 will assist in the future design of vaccines to protect against HCV infection.

4/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10540796 20084581 PMID: 10619563

The expression of **TAPA** (CD81) correlates with the reactive response of astrocytes in the developing rat CNS.

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Department of Physiological Optics, University of Alabama at Birmingham, 35294, USA.

Experimental neurology (UNITED STATES) Dec **1999**, 160 (2) p460-8, ISSN 0014-4886 Journal Code: 0370712

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

During the development of the brain, astrocytes acquire the ability to become reactive and form a scar. This change in the astrocytes occurs at approximately the same time that there is a decrease in the regenerative capacity of the CNS. Previous work from our laboratory had revealed that **TAPA** (Target of Anti-Proliferative **Antibody** , also known as CD81) is associated with reactive gliosis and the glial scar. **TAPA** is a member of the tetraspan family of proteins that appears to be associated with the regulation of cellular behavior. In order to define the role of **TAPA** in relation to the developmentally regulated CNS response to injury, we examined the levels of **TAPA** and GFAP immunoreactivity in rat pups that received a penetrating cerebral cortical injury. All of the animals injured at postnatal day 9 (PND 9), PND 18, or as adults, exhibited reactive gliosis scar formation when they were sacrificed 10 days after the cortical injury. Of the nine animals injured at PND 2, only three displayed reactive gliosis and scar formation. The remaining six rat pups had either a modest gliotic response or no detectable gliosis. The level of **TAPA** at the site of injury mimicked the reactive gliosis as defined by GFAP immunoreactivity. In all of the rats with a glial scar, there was a dramatic upregulation of **TAPA** that is spatially restricted to the reactive astrocytes. These results suggest that the upregulation of **TAPA** is an integral component of glial scar formation.

4/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10523755 20059404 PMID: 10590270

Association of a tetraspanin CD9 with CD5 on the T cell surface: role of particular transmembrane domains in the association.

Toyo-oka K; Yashiro-Ohtani Y; Park C S; Tai X G; Miyake K; Hamaoka T; Fujiwara H

Department of Oncology, Biomedical Research Center, Osaka University Graduate School of Medicine 2-2, Yamada-oka, Suita, Osaka 565-0871, Japan.

International immunology (ENGLAND) Dec **1999**, 11 (12) p2043-52, ISSN 0953-8178 Journal Code: 8916182

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

CD9 is a member of the tetraspanin superfamily which is characterized by four transmembrane (TM) domains and associates with other surface molecules. This tetraspanin was recently found to be expressed on mature T cells. Here, we investigated which molecules associate with CD9 on T cells and which CD9 domains are required for the association. Immunoprecipitation of T cell lysates with anti-CD9 mAb followed by immunoblotting with mAb against various T cell molecules showed the association of CD9 with CD3, CD4, CD5, CD2, CD29 and CD44. Because association with CD5 was most prominent, we determined the role of CD9 TM or extracellular (EC) domains in the association with CD5. CD9 mutant genes lacking each domain were constructed and introduced into EL4 thymoma cells deficient in CD9 but expressing CD5. Among various types of stable EL4 transfectants, EL4 transfected with the mutant gene lacking TM domains (TM2/TM3) between two EC domains expressed a small amount of the relevant protein without showing

association with CD5. CD9(-)CD5(-) monkey COS-7 cells transfected with this mutant gene and the CD5 gene expressed both transfected gene products, but the association of these was not detected. EL4 cells transfected with a CD9/CD81 chimera gene (the CD9 gene containing TM2/TM3 of CD81) expressed the chimeric protein on the cell surface and showed association with CD5. These results suggest an essential role of particular CD9 TM domains in the surface expression of the CD9 molecule as well as the association with CD5.

4/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10397995 99389749 PMID: 10459022
Role of transmembrane 4 superfamily (TM4SF) proteins CD9 and CD81 in muscle cell fusion and myotube maintenance.
Tachibana I; Hemler M E
Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of cell biology (UNITED STATES) Aug 23 **1999**, 146 (4) p893-904, ISSN 0021-9525 Journal Code: 0375356
Contract/Grant No.: GM38903; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The role of transmembrane 4 superfamily (TM4SF) proteins during muscle cell fusion has not been investigated previously. Here we show that the appearance of TM4SF protein, CD9, and the formation of CD9-beta1 integrin complexes were both regulated in coordination with murine C2C12 myoblast cell differentiation. Also, anti-CD9 and anti-CD81 monoclonal **antibodies** substantially inhibited and delayed conversion of C2C12 cells to elongated myotubes, without affecting muscle-specific protein expression. Studies of the human myoblast-derived RD sarcoma cell line further demonstrated that TM4SF proteins have a role during muscle cell fusion. Ectopic expression of CD9 caused a four- to eightfold increase in RD cell syncytia formation, whereas anti-CD9 and anti-CD81 **antibodies** markedly delayed RD syncytia formation. Finally, anti-CD9 and anti-CD81 monoclonal **antibodies** triggered apoptotic degeneration of C2C12 cell myotubes after they were formed. In summary, TM4SF proteins such as CD9 and CD81 appear to promote muscle cell fusion and support myotube maintenance.

4/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10347258 99329203 PMID: 10400776
Functional analysis of cell surface-expressed hepatitis C virus E2 glycoprotein.
Flint M; Thomas J M; Maidens C M; Shotton C; Levy S; Barclay W S; McKeating J A
School of Animal and Microbial Sciences, University of Reading, Whiteknights, Reading RG6 6AJ, United Kingdom.
Journal of virology (UNITED STATES) Aug **1999**, 73 (8) p6782-90, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: CA 34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) glycoproteins E1 and E2, when expressed in eukaryotic cells, are retained in the endoplasmic reticulum (ER). C-terminal truncation of E2 at residue 661 or 715 (position on the polyprotein) leads to secretion, consistent with deletion of a proposed hydrophobic transmembrane anchor sequence. We demonstrate cell surface

expression of a chimeric glycoprotein consisting of E2 residues 384 to 661 fused to the transmembrane and cytoplasmic domains of influenza A virus hemagglutinin (HA), termed E2661-HATMCT. The E2661-HATMCT chimeric glycoprotein was able to bind a number of conformation-dependent monoclonal **antibodies** and a recombinant soluble form of CD81, suggesting that it was folded in a manner comparable to "native" E2. Furthermore, cell surface-expressed E2661-HATMCT demonstrated pH-dependent changes in antigen conformation, consistent with an acid-mediated fusion mechanism. However, E2661-HATMCT was unable to induce cell fusion of CD81-positive HEK cells after neutral- or low-pH treatment. We propose that a stretch of conserved, hydrophobic amino acids within the E1 glycoprotein, displaying similarities to flavivirus and paramyxovirus fusion peptides, may constitute the HCV fusion peptide. We demonstrate that influenza virus can incorporate E2661-HATMCT into particles and discuss experiments to address the relevance of the E2-CD81 interaction for HCV attachment and entry.

4/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10265392 99247901 PMID: 10229664
Selective tetraspan-integrin complexes (CD81/alpha4beta1, CD151/alpha3beta1, CD151/alpha6beta1) under conditions disrupting tetraspan interactions.
Serru V; Le Naour F; Billard M; Azorsa D O; Lanza F; Boucheix C; Rubinstein E
INSERM U268, Hopital Paul Brousse, 94807 Villejuif Cedex, France.
Biochemical journal (ENGLAND) May 15 **1999**, 340 (Pt 1) p103-11,
ISSN 0264-6021 Journal Code: 2984726R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The tetraspans are molecules with four transmembrane domains which are engaged in multimolecular complexes (the tetraspan web) containing a subset of beta1 integrins (in particular alpha3beta1, alpha4beta1 and alpha6beta1), MHC antigens and several unidentified molecules. The molecules associated with tetraspans are readily detected after immunoprecipitation performed in mild detergents such as Brij 97 or CHAPS. In this study we show that another classical mild detergent, digitonin, dissociated most of these associated molecules, including integrins, from the tetraspans CD9, CD37, CD53, CD63, CD82, Co-029, Talla-1 and NAG-2. In contrast, reciprocal immunoprecipitations from various cell lines demonstrated that two other tetraspans, CD81 and CD151, formed complexes with integrins not disrupted by digitonin. These complexes were CD81/alpha4beta1, CD151/alpha3beta1 and CD151/alpha6beta1. Furthermore, a new anti-CD151 monoclonal **antibody** (mAb), TS151r, was shown to have a restricted pattern of expression, inversely related to the sum of the levels of expression of alpha6beta1 and alpha3beta1. This mAb was unable to co-precipitate integrins in digitonin, suggesting that its epitope is blocked by the association with integrins. Indeed, the binding of TS151r to the cell surface was quantitatively diminished following alpha3beta1 overexpression. Altogether, these data suggest that, among tetraspans, CD81 interacts directly with the integrin alpha4beta1, and CD151 interacts directly with integrins alpha3beta1 and alpha6beta1. Because all tetraspan-tetraspan associations are disrupted by digitonin, it is likely that the other tetraspans interact indirectly with integrins, through interactions with CD81 or CD151.

4/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10092974 99077164 PMID: 9862348
Gamma-glutamyl transpeptidase, an ecto-enzyme regulator of intracellular

redox potential, is a component of TM4 signal transduction complexes.
Nichols T C; Guthridge J M; Karp D R; Molina H; Fletcher D R; Holers V M
Department of Medicine, University of Colorado Health Sciences Center, Denver 80262, USA.
European journal of immunology (GERMANY) Dec **1998**, 28 (12) p4123-9, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD21 (C3dg/EBV receptor) is physically associated on B cells with a complex of proteins that includes CD19 and the widely distributed tetraspan 4 (TM4) family protein CD81 as well as other TM4 proteins (CD53, CD37 and CD82). Monoclonal **antibodies** (mAb) were generated that blocked homotypic adhesion induced by CD21 ligands in the human B cell line Balm-1. One inhibitory mAb (3A8) was found to recognize the ecto-enzyme gamma-glutamyl transpeptidase (GGT), a membrane protein involved in recycling extracellular glutathione and regulating intracellular redox potential. Molecular associations between GGT and TM4 proteins CD81, CD53 and CD82, in addition to CD21 and CD19, were detected by co-precipitation and co-capping analysis. GGT is expressed on several B and T cell lines independently of CD21 expression. These results demonstrate that GGT is a component of widely distributed TM4 complexes, and that on B cells the GGT-containing TM4 complexes also contain CD19 and CD21.

4/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10037036 99011351 PMID: 9794763
Binding of hepatitis C virus to CD81.
Pileri P; Uematsu Y; Campagnoli S; Galli G; Falugi F; Petracca R; Weiner A J; Houghton M; Rosa D; Grandi G; Abrignani S
IRIS, Chiron, Siena 53100, Italy.
Science (UNITED STATES) Oct 30 **1998**, 282 (5390) p938-41, ISSN 0036-8075 Journal Code: 0404511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chronic hepatitis C virus (HCV) infection occurs in about 3 percent of the world's population and is a major cause of liver disease. HCV infection is also associated with cryoglobulinemia, a B lymphocyte proliferative disorder. Virus tropism is controversial, and the mechanisms of cell entry remain unknown. The HCV envelope protein E2 binds human CD81, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes. Binding of E2 was mapped to the major extracellular loop of CD81. Recombinant molecules containing this loop bound HCV and **antibodies** that neutralize HCV infection in vivo inhibited virus binding to CD81 in vitro.

4/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09873846 98287686 PMID: 9624590
Expression of rat target of the antiproliferative **antibody** (**TAPA**) in the developing brain.
Sullivan C D; Geisert E E
Department of Anatomy and Neurobiology, University of Tennessee, Memphis College of Medicine 38163, USA.
Journal of comparative neurology (UNITED STATES) Jul 6 **1998**, 396 (3) p366-80, ISSN 0021-9967 Journal Code: 0406041
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The present study defines the expression pattern of **TAPA** (target of the antiproliferative **antibody**, also known as CD81) in the developing rat brain. **TAPA** is a member of the tetramembrane spanning family of proteins, and like other members of this family it appears to be associated with the stabilization of cellular contacts (Geisert et al. [1996] J. Neurosci. 16:5478-5487). On immunoblots of the brain, **TAPA** is present in higher levels than any other tissue examined: muscle, tendon, peripheral nerve, cartilage, liver, kidney, skin, and testicle. Immunohistochemical methods were used to define the distribution of **TAPA** in the brain. This protein is expressed by ependyma, choroid plexus, astrocytes, and oligodendrocytes. **TAPA** is dramatically upregulated during early postnatal development, at the time of glial birth and maturation. At embryonic day 18, the levels of **TAPA** are low, with most of the immunoreaction product being associated with the ependyma, choroid plexus, and the glia limitans. As development continues, the amount of **TAPA** expressed in the brain increases, and at postnatal day 14 the levels approach those of the adult. This increase in the levels of **TAPA** at postnatal day 14 is due to upregulation in the gray matter and white matter. Thus, **TAPA** is found in all glial cells, and the level of this protein correlates with their maturation.

4/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09845452 98259413 PMID: 9597125

CD81 (**TAPA**-1): a molecule involved in signal transduction and cell adhesion in the immune system.

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Annual review of immunology (UNITED STATES) **1998**, 16 p89-109, ISSN 0732-0582 Journal Code: 8309206
Contract/Grant No.: 5T32CA9302; CA; NCI; CA34233; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

CD81 (**TAPA** -1) is a widely expressed cell-surface protein involved in an astonishing variety of biologic responses. It has been cloned independently several times for different functional effects and is reported to influence adhesion, morphology, activation, proliferation, and differentiation of B, T, and other cells. On B cells CD81 is part of a complex with CD21, CD19, and Leu13. This complex reduces the threshold for B cell activation via the B cell receptor by bridging Ag specific recognition and CD21-mediated complement recognition. Similarly on T cells CD81 associates with CD4 and CD8 and provides a costimulatory signal with CD3. In fetal thymic organ culture, mAb to CD81 block maturation of CD4-CD8- thymocytes, and expression of CD81 on CHO cells endows those cells with the ability to support T cell maturation. However, CD81-deficient mice express normal numbers and subsets of T cells. These mice do exhibit diminished **antibody** responses to protein antigens. CD81 is also physically and functionally associated with several integrins. Anti-CD81 can activate integrin alpha 4 beta 1 (VLA-4) on B cells, facilitating their adhesion to tonsilar interfollicular stroma. Similarly, anti-CD81 can activate alpha L beta 2 (LFA-1) on human thymocytes. CD81 can also affect cognate B-T cell interactions because anti-CD81 increases IL-4 synthesis by T cells responding to antigen presented by B cells but not by monocytes. The tetraspanin superfamily (or TM4SF) includes CD81, CD9, CD37, CD53, CD63, CD82, CD151, and an increasing number of additional proteins. Like CD81, several tetraspanins are involved in cell adhesion, motility, and

metastasis, as well as cell activation and signal transduction.

4/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09845446 98259429 PMID: 9597141
The role of complement and complement receptors in induction and regulation of immunity.
Carroll M C
Department of Pathology, Harvard University Medical School, Boston, Massachusetts 02115, USA. mcarroll@warren.med.harvard.edu
Annual review of immunology (UNITED STATES) **1998**, 16 p545-68, ISSN 0732-0582 Journal Code: 8309206
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Covalent attachment of activated complement C3 (C3d) to antigen links innate and adaptive immunity by targeting antigen to follicular dendritic cells (FDC) and B cells via specific receptors CD21 and CD35. Recent characterization of knockout mice deficient in complement components C3, C4, or the receptors CD21 and CD35 as well as biochemical studies of the CD21/CD19/**Tapa** -1 coreceptor on B cells have helped to elucidate the mechanism of complement regulation of both B-1 and B-2 lymphocytes. Interestingly, natural **antibody** of the adaptive immune system provides a major recognition role in activation of the complement system, which in turn enhances activation of antigen-specific B cells. Enhancement of the primary and secondary immune response to T-dependent antigens is mediated by coligation of the coreceptor and the B cell antigen receptor, which dramatically increases follicular retention and B cell survival within the germinal center. Most recent evidence suggests that complement also regulates elimination of self-reactive B cells, as breeding of mice that are deficient in C4 or CD21/CD35 with the lupus-prone strain of lpr mice demonstrates an exacerbation of disease due to an increase in autoantibodies.

4/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09807389 98234412 PMID: 9566977
Regulation of endothelial cell motility by complexes of tetraspan molecules CD81/**TAPA** -1 and CD151/PETA-3 with alpha3 beta1 integrin localized at endothelial lateral junctions.
Yanez-Mo M; Alfranca A; Cabanas C; Marazuela M; Tejedor R; Ursa M A; Ashman L K; de Landazuri M O; Sanchez-Madrid F
Servicio de Inmunologia, Hospital de la Princesa, Universidad Autonoma de Madrid.
Journal of cell biology (UNITED STATES) May 4 **1998**, 141 (3) p791-804, ISSN 0021-9525 Journal Code: 0375356
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cell-to-cell junction structures play a key role in cell growth rate control and cell polarization. In endothelial cells (EC), these structures are also involved in regulation of vascular permeability and leukocyte extravasation. To identify novel components in EC intercellular junctions, mAbs against these cells were produced and selected using a morphological screening by immunofluorescence microscopy. Two novel mAbs, LIA1/1 and VJ1/16, specifically recognized a 25-kD protein that was selectively localized at cell-cell junctions of EC, both in the primary formation of cell monolayers and when EC reorganized in the process of wound healing.

This antigen corresponded to the recently cloned platelet-endothelial tetraspan antigen CD151/PETA-3 (platelet-endothelial tetraspan antigen-3), and was consistently detected at EC cell-cell contact sites. In addition to CD151/PETA-3, two other members of the tetraspan superfamily, CD9 and CD81/ **TAPA**-1 (target of antiproliferative **antibody**-1), localized at endothelial cell-to-cell junctions. Biochemical analysis demonstrated molecular associations among tetraspan molecules themselves and those of CD151/ PETA-3 and CD9 with alpha3 beta1 integrin. Interestingly, mAbs directed to both CD151/PETA-3 and CD81/ **TAPA** -1 as well as mAb specific for alpha3 integrin, were able to inhibit the migration of ECs in the process of wound healing. The engagement of CD151/PETA-3 and CD81/ **TAPA** -1 inhibited the movement of individual ECs, as determined by quantitative time-lapse video microscopy studies. Furthermore, mAbs against the CD151/PETA-3 molecule diminished the rate of EC invasion into collagen gels. In addition, these mAbs were able to increase the adhesion of EC to extracellular matrix proteins. Together these results indicate that CD81/ **TAPA** -1 and CD151/PETA-3 tetraspan molecules are components of the endothelial lateral junctions implicated in the regulation of cell motility, either directly or by modulation of the function of the associated integrin heterodimers.

4/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09766049 98189267 PMID: 9514697
Functional analysis of four tetraspans, CD9, CD53, CD81, and CD82, suggests a common role in costimulation, cell adhesion, and migration: only CD9 upregulates HB-EGF activity.
Lagaudriere-Gesbert C; Le Naour F; Lebel-Binay S; Billard M; Lemichez E; Boquet P; Boucheix C; Conjeaud H; Rubinstein E
INSERM U283, Hopital Cochin, Paris, France.
Cellular immunology (UNITED STATES) Dec 15 **1997**, 182 (2) p105-12, ISSN 0008-8749 Journal Code: 1246405
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Molecules of the tetraspan superfamily are engaged in multimolecular complexes containing other proteins such as beta 1 integrins and MHC antigens. Although their functions are not clear, they have been suggested to play a role in cell adhesion and migration, signal transduction, and costimulation. We have in this paper directly compared the functional properties of four tetraspans, CD9, CD53, CD81, and CD82. mAbs to any of these molecules were able to deliver a costimulatory signal for CD3-mediated activation of the T cell line Jurkat. CD82 mAbs were the most efficient in triggering this effect. Moreover, engagement of CD9, CD81, and CD82 induced the homotypic aggregation of the megakaryocytic cell line HEL, and inhibited the migration of this cell line. Similar results were obtained with the preB cell line NALM-6 using the CD9 and CD81 mAbs. The CD81 mAb 5A6 produced the strongest effects. Therefore, the tetraspans are recognized by mAbs which produce similar effects on the same cell lines. This is consistent with the tetraspans being included in large molecular complexes and possibly forming a tetraspan network (the tetraspan web). We also demonstrate that the tetraspans are likely to keep specific functional properties inside this network. Indeed, we have demonstrated that the human CD9 is able, like the monkey molecule, to upregulate the activity of the transmembrane precursor of heparin-binding EGF as a receptor for the diphtheria toxin when cotransfected in murine LM cells. Neither CD81, nor CD82 had such activity. By using chimeric CD9/CD81 molecules we demonstrate that this activity requires the second half of CD9, which contains the large extracellular loop, the fourth transmembrane region, and the last short cytoplasmic domain.

4/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09724524 98151534 PMID: 9482907
CD81 on B cells promotes interleukin 4 secretion and **antibody** production during T helper type 2 immune responses.
Maecker H T; Do M S; Levy S
Department of Medicine/Oncology, Stanford University Medical Center, Stanford, CA 94305, USA. hmaecker@cmgm.stanford.edu
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 3 **1998**, 95 (5) p2458-62, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: CA 34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Mice lacking CD81 (**TAPA** -1), a widely expressed tetraspanin molecule, have impaired **antibody** responses to protein antigens. This defect is specific to antigens that preferentially stimulate a T helper 2 response (ovalbumin or keyhole limpet hemocyanin in alum) and is only seen with T cell-dependent antigens. Absence of CD81 on B cells is sufficient to cause the defect. Also, antigen-specific interleukin (IL) 4 production is greatly reduced in the spleen and lymph nodes of CD81-null mice compared with heterozygous littermates. Thus, expression of CD81 on B cells is critical for inducing optimal IL-4 and **antibody** production during T helper 2 responses. These findings suggest that CD81 may interact with a ligand on T cells to signal IL-4 production. By using a soluble form of CD81 as a probe, a putative ligand for CD81 was identified on a subset of B and T cells. Two possible models for the interaction of CD81 on B cells with a potential ligand on either B or T cells are proposed.

4/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09720087 98153249 PMID: 9485486
The target of the antiproliferative **antibody** (**TAPA**) in the normal and injured rat retina.
Clarke K; Geisert E E
Department of Anatomy and Neurobiology, University of Tennessee, Memphis College of Medicine, Memphis TN 38163, USA.
Molecular vision computer file (UNITED STATES) Feb 10 **1998**, 4 p3, ISSN 1090-0535 Journal Code: 9605351
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: The target of the antiproliferative **antibody** (**TAPA**, CD81) is a member of the tetramembrane spanning superfamily of proteins and appears to be involved in the regulation of mitotic activity and the stabilization of cellular contacts [J Neurosci 1996; 16:5478-5487]. The present study examines the distribution of this protein in the normal rat retina and its role in reactive gliosis occurring after retinal injury. METHODS: An immunoblot was used to define the relative level of **TAPA** in the normal rat retina. The distribution of the protein was examined using indirect immunohistochemical methods. Both of these methods were used to define the upregulation of **TAPA** in the rat retina injured with a needle scrape. RESULTS: The immunohistochemical analysis of the retina shows that **TAPA** is found in all layers of the normal retina with a distinct lack of labeling in the inner and outer segments of the photoreceptors. After retinal injury, a dramatic upregulation of **TAPA** was observed. The immunohistochemistry also revealed a pattern of

expression similar to that observed in the normal retina with two notable exceptions: (1) small finger-like projections extending down into the outer segments are immunopositive, and (2) the elevated levels of **TAPA** can be seen outlining cell bodies in the outer nuclear layer and the ganglion cell layer. CONCLUSIONS: **TAPA** is found in the normal rat retina and there is a dramatic upregulation of this protein following injury. The distribution of the protein within the retina is consistent with its expression in retinal glia, the Muller cells which span the thickness of the retina, and astrocytes found in the ganglion cell layer. These data suggest that **TAPA** may play a role in the proliferative response of non-neuronal cells that occurs following a mechanical injury to the retina.

4/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09598752 98030601 PMID: 9360996
NAG-2, a novel transmembrane-4 superfamily (TM4SF) protein that complexes with integrins and other TM4SF proteins.
Tachibana I; Bodorova J; Berditchevski F; Zutter M M; Hemler M E
Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of biological chemistry (UNITED STATES) Nov 14 **1997**, 272 (46) p29181-9, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: CA70275; CA; NCI; GM38903; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Transmembrane-4 superfamily (TM4SF) proteins form complexes with integrins and other cell-surface proteins. To further characterize the major proteins present in a typical TM4SF protein complex, we raised monoclonal **antibodies** against proteins co-immunoprecipitated with CD81 from MDA-MB-435 breast cancer cells. Only two types of cell-surface proteins were recognized by our 35 selected **antibodies** . These included an integrin (alpha6beta1) and three different TM4SF proteins (CD9, CD63, and NAG-2). The protein NAG-2 (novel antigen-2) is a previously unknown 30-kDa cell-surface protein. Using an expression cloning protocol, cDNA encoding NAG-2 was isolated. When aligned with other TM4SF proteins, the deduced amino acid sequence of NAG-2 showed most identity (34%) to CD53. Flow cytometry, Northern blotting, and immunohistochemistry showed that NAG-2 is widely present in multiple tissues and cell types but is absent from brain, lymphoid cells, and platelets. Within various tissues, strongest staining was seen on fibroblasts, endothelial cells, follicular dendritic cells, and mesothelial cells. In nonstringent detergent, NAG-2 protein was co-immunoprecipitated with other TM4SF members (CD9 and CD81) and integrins (alpha3beta1 and alpha6beta1). Also, two-color immunofluorescence showed that NAG-2 was co-localized with CD81 on the surface of spread HT1080 cells. These results confirm the presence of NAG-2 in specific TM4SF.TM4SF and TM4SF-integrin complexes.

4/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09594139 98028160 PMID: 9362067
Integrin alpha 6A beta 1 induces CD81-dependent cell motility without engaging the extracellular matrix migration substrate.
Domanico S Z; Pelletier A J; Havran W L; Quaranta V
Department of Cell Biology, Scripps Research Institute, La Jolla, California 92037, USA.
Molecular biology of the cell (UNITED STATES) Nov **1997**, 8 (11) p2253-65, ISSN 1059-1524 Journal Code: 9201390
Contract/Grant No.: CA-47858; CA; NCI; DE-10063; DE; NIDCR

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

It is well established that integrins and extracellular matrix (ECM) play key roles in cell migration, but the underlying mechanisms are poorly defined. We describe a novel mechanism whereby the integrin alpha 6 beta 1, a laminin receptor, can affect cell motility and induce migration onto ECM substrates with which it is not engaged. By using DNA-mediated gene transfer, we expressed the human integrin subunit alpha 6A in murine embryonic stem (ES) cells. ES cells expressing alpha 6A (ES6A) at the surface dimerized with endogenous beta 1, extended numerous filopodia and lamellipodia, and were intensely migratory in haptotactic assays on laminin (LN)-1. Transfected alpha 6A was responsible for these effects, because cells transfected with control vector or alpha 6B, a cytoplasmic domain alpha 6 isoform, displayed compact morphology and no migration, like wild-type ES cells. The ES6A migratory phenotype persisted on fibronectin (Fn) and Ln-5. Adhesion inhibition assays indicated that alpha 6 beta 1 did not contribute detectably to adhesion to these substrates in ES cells. However, anti-alpha 6 **antibodies** completely blocked migration of ES6A cells on Fn or Ln-5. Control experiments with monensin and anti-ECM **antibodies** indicated that this inhibition could not be explained by deposition of an alpha 6 beta 1 ligand (e.g., Ln-1) by ES cells. Cross-linking with secondary **antibody** overcame the inhibitory effect of anti-alpha 6 **antibodies** , restoring migration or filopodia extension on Fn and Ln-5. Thus, to induce migration in ES cells, alpha 6A beta 1 did not have to engage with an ECM ligand but likely participated in molecular interactions sensitive to anti-alpha 6 beta 1 **antibody** and mimicked by cross-linking. **Antibodies** to the tetraspanin CD81 inhibited alpha 6A beta 1-induced migration but had no effect on ES cell adhesion. It is known that CD81 is physically associated with alpha 6 beta 1, therefore our results suggest a mechanism by which interactions between alpha 6A beta 1 and CD81 may up-regulate cell motility, affecting migration mediated by other integrins.

4/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09590301 98021456 PMID: 9380722

Impaired CD19 expression and signaling, enhanced **antibody** response to type II T independent antigen and reduction of B-1 cells in CD81-deficient mice.

Tsitsikov E N; Gutierrez-Ramos J C; Geha R S
Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Sep 30 **1997**, 94 (20) p10844-9, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: HD 17461; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The tetraspanin CD81 is ubiquitously expressed and associated with CD19 on B lymphocytes and with CD4 and CD8 on T lymphocytes. Analysis of mice with disrupted CD81 gene reveals normal T cells but a distinct abnormality in B cells consisting of decreased expression of CD19 and severe reduction in peritoneal B-1 cells. CD81-deficient B cells responded normally to surface IgM crosslinking, but had severely impaired calcium influx following CD19 engagement. CD81-deficient mice had increased serum IgM and IgA and an exaggerated **antibody** response to the type II T independent antigen TNP-Ficoll. These results suggest that CD81 is important for CD19 signaling and B cell function.

4/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09559252 97477414 PMID: 9334370
Negative regulation of Fc epsilon RI-mediated degranulation by CD81.
Fleming T J; Donnadieu E; Song C H; Laethem F V; Galli S J; Kinet J P
Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, USA.
Journal of experimental medicine (UNITED STATES) Oct 20 **1997**, 186 (8) p1307-14, ISSN 0022-1007 Journal Code: 2985109R
Contract/Grant No.: AI/CA-23990; AI; NIAID; CA/AI-72074; CA; NCI; GM-53950; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Signaling through the high affinity receptor for immunoglobulin E (Fc epsilon RI) results in the coordinate activation of tyrosine kinases before calcium mobilization. Receptors capable of interfering with the signaling of antigen receptors, such as Fc epsilon RI, recruit tyrosine and inositol phosphatases that results in diminished calcium mobilization. Here, we show that **antibodies** recognizing CD81 inhibit Fc epsilon RI-mediated mast cell degranulation but, surprisingly, without affecting aggregation-dependent tyrosine phosphorylation, calcium mobilization, or leukotriene synthesis. Furthermore, CD81 **antibodies** also inhibit mast cell degranulation in vivo as measured by reduced passive cutaneous anaphylaxis responses. These results reveal an unsuspected calcium-independent pathway of antigen receptor regulation, which is accessible to engagement by membrane proteins and on which novel therapeutic approaches to allergic diseases could be based.

4/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09497248 97392451 PMID: 9250665
Normal development but differentially altered proliferative responses of lymphocytes in mice lacking CD81.
Miyazaki T; Muller U; Campbell K S
Basel Institute for Immunology, Switzerland. miyazaki@bii.ch
EMBO journal (ENGLAND) Jul 16 **1997**, 16 (14) p4217-25, ISSN 0261-4189 Journal Code: 8208664
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD81 (**TAPA** -1) is a member of the transmembrane 4 superfamily (TM4SF) which is expressed on the cell surface of most cells of the body throughout their cellular differentiation. It has been recognized in several cell surface complexes of lymphocytes, suggesting that it may have diverse roles in lymphocyte development and activation regulation. Mice with a CD81 null mutation revealed normal T- and conventional B-cell development, although CD19 expression on B cells was dull and B-1 cells were reduced in number. However, both T and B cells of mutant mice exhibited strikingly enhanced proliferation in response to various types of stimuli. Interestingly, while proliferative responses of T cells following T-cell antigen receptor (TCR) engagement was enhanced in the absence of CD81, B-cell proliferation in response to B-cell antigen-receptor (BCR) cross-linking was severely impaired. Despite these altered proliferative responses, both tyrosine phosphorylation and intracellular calcium flux in response to cross-linking of cell surface antigen receptors were normal in mutant mice, reflecting apparently normal initial signaling of antigen

receptors. In conclusion, though CD81 is not essential for normal T- and conventional B-cell development, it plays key roles in controlling lymphocyte homeostasis by regulating lymphocyte proliferation in distinct manners, dependent on the context of stimulation.

4/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09486509 97389378 PMID: 9265505
Synergy between anti-CD40 MAb and Epstein-Barr virus in activation and transformation of human B lymphocytes.
Tsuchiyama L; Kieran J; Boyle P; Wetzel G D
Preclinical Biology Research, Bayer Corp., Berkeley, CA 94701, USA.
Human antibodies (UNITED STATES) **1997**, 8 (1) p43-7, ISSN 1093-2607 Journal Code: 9711270
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
For human B lymphocytes, Epstein-Barr virus (EBV) is a polyclonal activator, inducing both proliferation and Ig secretion. It is also a transforming virus capable of generating immortalized B cell lines. These early and late functions of EBV are not apparently connected. The receptor for EBV, CD21, also serves as a receptor for some complement components and is called CR2. This molecule associates with CD19 and **TAPA**-1 on the surface of B cells. This complex is involved in signaling B cells and participates in many responses. We have observed that simultaneous ligation of CD40 and the CD21 complex, by exposure to anti-CD40 MAbs and EBV, enhances both the short-term proliferation as well as the long-term transformation rate of human B lymphocytes. B cell proliferation shows synergy between anti-CD40 MAb and EBV. CD19 also appears to be involved in the synergistic activation of B cells through CD40 and CD21, since ligation of CD19 with anti-CD19 MAbs, either prior to or concomitant with exposure to anti-CD40 and EBV, markedly inhibits both proliferation and subsequent B cell transformation. These observations do not elucidate the mechanisms of B cell transformation employed by EBV but the do suggest a relationship between early proliferation and later transformation induced by the virus. Anti-CD40 enhances both these effects and anti-CD19 is capable of inhibiting both.

4/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09483401 97364299 PMID: 9220577
Cross-reactivity of monoclonal **antibodies** to defined human leucocyte differentiation antigens with bovine cells.
Sopp P; Howard C J
Institute for Animal Health, Compton Laboratory, Newbury, Berkshire, UK. sopp@bbsrc.ac.uk
Veterinary immunology and immunopathology (NETHERLANDS) May **1997**, 56 (1-2) p11-25, ISSN 0165-2427 Journal Code: 8002006
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Thirty-seven subpanels of monoclonal **antibodies** (mAbs) included within the Vth International Workshop on Human Leucocyte Differentiation Antigens (Vth Workshop) were assayed for reactivity with bovine peripheral blood leucocytes. Sixty-five of the 772 mAbs (8.4%) stained bovine cells. mAbs from each of the 27 different CD groups that contained a mAb reacting with cattle were further investigated to compare the cellular expression of the antigen in cattle with that reported for the different CD antigens in

humans. Two-colour immunofluorescence staining of the Vth Workshop mAbs against characterized bovine leucocyte subpopulation markers that identified monocytes, B cells, CD4, CD8 and WC1 +T cells were used for these analyses. Eighteen of the mAbs to different human CD antigens (CD11a, CD14, CD18, CD21, CD27, CD29, CD49a, CD49b, CD49d, CD49e, CD51, CD61, CD62L, CD62P, CD63, CDw78, CD98, CD100) stained bovine antigens with an almost identical cellular distribution to that reported in humans. This implies that these mAb react with the homologous cattle molecules. Nine mAbs (CD35, CD37, CD49c, CD50, CD54, CD66, CD81, CD88, CD102) stained bovine cells but the cellular distribution of the bovine antigen was different to that reported in humans implying either a different cellular distribution for these antigens in cattle or a reaction with a different molecule. The investigation has allowed the identification of several bovine homologues of human CD antigens that have not been previously defined in cattle and the cross-reacting mAbs will be valuable reagents for future investigations of bovine immunology.

4/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09375017 97272087 PMID: 9126932
Normal lymphocyte development but delayed humoral immune response in CD81-null mice.
Maecker H T; Levy S
Department of Medicine and Oncology, Stanford University Medical Center, California 94305, USA.
Journal of experimental medicine (UNITED STATES) Apr 21 **1997**, 185 (8) p1505-10, ISSN 0022-1007 Journal Code: 2985109R
Contract/Grant No.: CA 34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD81 is a cell surface molecule expressed on many cell types and associated with the CD19/CD21/Leu13 signal-transducing complex on B cells. A recent report implies that CD81 expression on thymic stromal cells is important in the maturation of thymocytes from CD4-CD8- to CD4+CD8+. However, we have produced CD81-null mice by gene targeting, and find that they undergo normal development of thymocytes and express normal numbers of T cells. B cells are also found in normal numbers in the spleen, blood, and peritoneal cavity of CD81-null mice, but they express a lower level of CD19 compared to heterozygous littermates. Finally, early **antibody** responses to the protein antigen ovalbumin are weaker in CD81-null mice compared to their heterozygous littermates. This is consistent with the proposed role of the CD19/CD21/CD81-signaling complex in lowering the threshold for B cell responses. These results show that CD81 is not required for maturation of T cells, but is important for optimal expression of CD19 on B cells and optimal stimulation of **antibody** production.

4/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09274047 97160557 PMID: 9006891
A novel link between integrins, transmembrane-4 superfamily proteins (CD63 and CD81), and phosphatidylinositol 4-kinase.
Berditchevski F; Tolias K F; Wong K; Carpenter C L; Hemler M E
Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of biological chemistry (UNITED STATES) Jan 31 **1997**, 272 (5) p2595-8, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: GM38903; GM; NIGMS; GM54387; GM; NIGMS
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Enzymatic and immunochemical assays show a phosphatidylinositol 4-kinase in novel and specific complexes with proteins (CD63 and CD81) of the transmembrane 4 superfamily (TM4SF) and an integrin (alpha3beta1). The size (55 kDa) and other properties of the phosphatidylinositol 4-kinase (PI 4-K) (stimulated by nonionic detergent, inhibited by adenosine, inhibited by monoclonal **antibody** 4CG5) are consistent with PI 4-K type II. Not only was PI 4-K associated with alpha3beta1-CD63 complexes in alpha3-transfected K562 cells, but also it could be co-purified from CD63 in untransfected K562 cells lacking alpha3beta1. Thus, TM4SF proteins may link PI 4-K activity to the alpha3beta1 integrin. The alpha5beta1 integrin, which does not associate with TM4SF proteins, was not associated with PI 4-K. Notably, alpha3beta1-CD63-CD81-PI 4-K complexes are located in focal complexes at the cell periphery rather than in focal adhesions. The novel linkage between integrins, transmembrane 4 proteins, and phosphoinositide signaling at the cell periphery may play a key role in cell motility and provides a signaling pathway distinct from conventional integrin signaling through focal adhesion kinase.

4/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09171677 97079163 PMID: 8920895

CD81 expressed on human thymocytes mediates integrin activation and interleukin 2-dependent proliferation.

Todd S C; Lipps S G; Crisa L; Salomon D R; Tsoukas C D

Department of Biology and Molecular Biology Institute, San Diego State University, California 92182-4614, USA.

Journal of experimental medicine (UNITED STATES) Nov 1 **1996**, 184 (5) p2055-60, ISSN 0022-1007 Journal Code: 2985109R

Contract/Grant No.: GM39518; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Lymphocyte recognition of antigen by the antigen-specific T cell receptor (TCR) and coreceptor complexes rapidly alters the cell's adhesive properties facilitating high avidity cell-ligand interactions necessary for lymphocyte development and function. Here, we report the expression of CD81 (target of antiproliferative antigen [**TAPA**]-1) on human thymocytes and the physical association of CD81 with CD4 and CD8 T cell coreceptors. **Antibody** ligation of CD81 on thymocytes promotes the rapid induction of integrin-mediated cell-cell adhesion via lymphocyte function-associated molecule-1 (LFA-1). Cross-linking CD81 is also shown to be costimulatory with signaling through the TCR/CD3 complex inducing interleukin 2-dependent thymocyte proliferation. These data suggest that a CD81-mediated pathway in thymocytes is involved in the regulation of both cell adhesion and activation.

4/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09049834 96413238 PMID: 8816400

Supramolecular complexes of MHC class I, MHC class II, CD20, and tetraspan molecules (CD53, CD81, and CD82) at the surface of a B cell line JY.

Szollosi J; Horejsi V; Bene L; Angelisova P; Damjanovich S

Department of Biophysics, Medical University School, Debrecen, Hungary.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Oct 1 **1996**, 157 (7) p2939-46, ISSN 0022-1767 Journal Code: 2985117R

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The results of previous biochemical studies indicated that a fraction of MHC class II proteins is associated with four proteins of the tetraspan family, CD37, CD53, CD81, and CD82, and possibly with other membrane components, at the surface of JY B lymphoma cells. In the present communication we used a biophysical technique, namely the flow cytometric energy transfer method, to demonstrate the proximity of these molecules at the surface of the cells. Significant energy transfer (and, therefore, proximity within the 2-10 nm range) was observed between fluorescently labeled mAbs to DR, DQ, and the tetraspan molecules CD53, CD81, and CD82. Moreover, two other B cell surface molecules, CD20 and MHC class I, were found to be close to each other and to MHC class II and the tetraspan proteins, based on the observed high energy transfer efficiencies between the relevant fluorescently labeled mAbs. The character of simultaneous energy transfer from CD20, CD53, CD81, and CD82 to DR suggests that all these molecules are in a single complex with the DR molecules (or a complex of several DR molecules) rather than that each of them is separately associated with different DR molecules. Based on these data and previous biochemical results, a model is proposed predicting that the B cell membrane contains multicomponent supramolecular complexes consisting of at least two MHC class I and at least one DR, DQ, CD20, CD53, CD81, and CD82 molecules. Closer analysis of the energy transfer efficiencies makes it possible to suggest mutual orientations of the components within the complex. Participation of other molecules, not examined in this study (CD19 and CD37), in these supramolecular structures cannot be ruled out. These large assemblies of multiple B cell surface molecules may play a role in signaling through MHC molecules and in Ag presentation to T cells.

4/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09004192 96346153 PMID: 8757260

Astrocyte growth, reactivity, and the target of the antiproliferative **antibody**, **TAPA**.

Geisert E E; Yang L; Irwin M H

Department of Anatomy and Neurobiology, University of Tennessee, Memphis 38163, USA.

Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Sep 1 **1996**, 16 (17) p5478-87, ISSN 0270-6474 Journal Code: 8102140

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Reactive astrocytes form a scar after injury to the CNS that many investigators believe contributes to the lack of functional regeneration. In the present study, we identify an astrocytic membrane protein that appears to play an important role in reactive gliosis and scar formation. Cultures of rat astrocytes were used as a model system to produce and to screen monoclonal **antibodies** that would alter cell growth. One **antibody**, AMP1, was identified that depresses the mitotic activity of cultured glial cells and alters their morphology. Expression cloning reveals that the antigen on the external surface of the cultured glial cells has a high degree of homology with the human lymphocyte protein called Target of the Anti-Proliferative **Antibody** (**TAPA**-1; this rat protein will be referred to as rTAPA). rTAPA is a member of the tetramembrane-spanning superfamily of proteins and, as with other members of this family of proteins, rTAPA is associated with the regulation of cellular interactions and mitotic activity. After an injury to the cerebral cortex, there is a dramatic increase in AMP1 immunoreactivity that is

spatially restricted to the reactive astrocytes at the glial scar. This change represents an upregulation of a membrane protein, rTAPA, that is approximately equal to the increase observed for glial fibrillary acidic protein. The high levels of rTAPA at the site of CNS injury and the AMP1 **antibody** perturbation studies indicate that rTAPA may play a prominent role in the response of astrocytes to injury and in glial scar formation.

4/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09004133 96355008 PMID: 8757325
Transmembrane-4 superfamily proteins CD81 (**TAPA**-1), CD82, CD63, and CD53 specifically associated with integrin alpha 4 beta 1 (CD49d/CD29).
Mannion B A; Berditchevski F; Kraeft S K; Chen L B; Hemler M E
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Sep 1 **1996**, 157 (5) p2039-47, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: 5T32CA09172-20; CA; NCI; GM38318; GM; NIGMS; GM38903; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Anti-alpha 4 integrin mAb coprecipitated CD81 (**TAPA**-1), a 25-kDa cell surface protein, from various alpha 4 beta1 -positive hemopoietic cell lines, including Molt4, Jurkat, Ramos, and alpha 4-transfected K562 (KX4C4) cells. In reciprocal experiments, the integrin alpha 4 beta 1 (VLA4, CD49d/CD29) could be reprecipitated from CD81 immunoprecipitates. Anti-alpha 4 integrin mAb also coprecipitated CD81 from the alpha 4 beta 7-positive B cell line RPMI 8866. In contrast, no CD81 was identified in alpha 2 beta 1, alpha 5 beta 1, or alpha L beta 2 immunoprecipitates. Abs to other members of the transmembrane-4 superfamily, including CD53, CD63, and CD82, also coprecipitated alpha 4 beta 1. As shown by confocal microscopy, CD81 and CD82 colocalized with alpha 4 beta 1 in cell surface clusters. The cytoplasmic domain of the alpha 4 integrin was not necessary for alpha 4 beta 1/CD81 association, nor was the association influenced by divalent cations, EDTA, integrin-activating mAb, or alpha 4 subunit cleavage. Notably, two independent alpha 4 adhesion-deficient mutants (D346E and D408E) were deficient in their ability to associate with CD81. Thus, CD81 and other transmembrane-4 superfamily members may participate in functionally relevant interactions with alpha 4 beta 1 and other integrins.

4/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08937364 96305397 PMID: 8766544
Ligation of **TAPA**-1 (CD81) or major histocompatibility complex class II in co-cultures of human B and T lymphocytes enhances interleukin-4 synthesis by antigen-specific CD4+ T cells.
Secrist H; Levy S; DeKruyff R H; Umetsu D T
Department of Medicine, Stanford University School of Medicine, CA 94305, USA. levy@cmgm.stanford.edu
European journal of immunology (GERMANY) Jul **1996**, 26 (7) p1435-42, ISSN 0014-2980 Journal Code: 1273201
Contract/Grant No.: K07AI01026; AI; NIAID; R01AI24571; AI; NIAID; R01AI26322; AI; NIAID; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have previously shown that CD4+ T cells from allergic individuals are predisposed to producing interleukin (IL)-4 in response to allergens. IL-4 production could be modulated by antigen concentration as well as by the type of antigen-presenting cells (APC), with B lymphocytes inducing greater quantities of IL-4 than monocytes. Using this system we examined IL-4 synthesis after culture of CD4+ T cells with B cells, monocytes, or both, as APC in the presence of allergen and a monoclonal **antibody** against CD81 (**TAPA** -1), a member of the TM4 superfamily of proteins that regulates activation, proliferation and trafficking of B cells. Addition of anti-CD81 mAb during culture enhanced IL-4 synthesis by 2- to 70-fold over that using an isotype-matched control mAb. Furthermore, anti-CD81 mAb enhanced IL-4 synthesis in CD4+ T cells only when CD4+ T cells were cultured with B cells but not monocytes as APC, indicating that anti-CD81 mAb affected IL-4 synthesis in T cells via interactions with B cells. However, pretreatment of either population separately with anti-CD81 mAb prior to culture had no effect on subsequent IL-4 synthesis, suggesting a requirement for temporal or cooperative interactions between T and B lymphocytes. In addition, anti-CD81 mAb enhanced IL-4 production but reduced CD4+ T cell antigen-specific proliferation, demonstrating that IL-4 production and proliferation by CD4+ T cells were inversely related. Finally, mAb to major histocompatibility complex class II but not to anti-CD19 also enhanced IL-4 synthesis when B lymphocytes were used as APC. In all instances, enhancement of CD4+ IL-4 synthesis correlated with the presence of large cell aggregates in T-B lymphocyte cocultures. These results indicate that the capacity of B cells to induce IL-4 can be significantly enhanced by ligation of particular molecules on their surface and should aid in the design of treatments for diseases in which modulation of the cytokine profile would be beneficial.

4/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08902813 96249501 PMID: 8668914
Triggering of target of an antiproliferative **antibody**-1 (**TAPA** -1/CD81) up-regulates the release of tumour necrosis factor-alpha by the EBV-B lymphoblastoid cell line JY.
Altomonte M; Montagner R; Pucillo C; Maio M
Advanced Immunotherapy Unit, INRCCS-CRO, Department of Sciences and Biomedical Technologies, University of Udine, Italy.
Scandinavian journal of immunology (ENGLAND) Apr **1996**, 43 (4) p367-73, ISSN 0300-9475 Journal Code: 0323767
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Target of an antiproliferative **antibody**-1 (**TAPA**-1/CD81) has been shown to be non-covalently associated to HLA-DR antigens on the cell surface of B cells. In this study the authors report that triggering of CD81 by MoAb 5A6 or 1D6 significantly ($P < 0.05$) up-regulates the release of tumour necrosis factor-alpha (TNF-alpha) by the Epstein-Barr virus-positive (EBV)-B lymphoblastoid cell line JY. The accumulation of TNF-alpha in the culture medium of JY cells incubated with either anti-CD81 MoAb was found to be dose-dependent and similar to that obtained following crosslinking of HLA-DR antigens with MoAb L243. The effect of the combination of anti-CD81 and anti-HLA-DR MoAb on the release of TNF-alpha by JY cells was not synergistic or additive. In addition, the combination of anti-CD81 and anti-HLA-DR MoAb did not affect proliferation and homotypic aggregation of JY cells induced by each MoAb used alone. Both anti-CD81 or anti-HLA-DR MoAb induced protein tyrosine phosphorylation. However, different cytoplasmic proteins were phosphorylated following triggering of either molecule. Taken together, the data demonstrate that CD81 and HLA-DR antigens induce similar effector phenomena in the regulation of TNF-alpha release, homotypic aggregation and inhibition of JY

cell proliferation.

4/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08800174 96138400 PMID: 8539618
A role for CD81 in early T cell development.
Boismenu R; Rhein M; Fischer W H; Havran W L
Department of Immunology, Scripps Research Institute, La Jolla, CA 92037, USA.
Science (UNITED STATES) Jan 12 **1996**, 271 (5246) p198-200, ISSN 0036-8075 Journal Code: 0404511
Contract/Grant No.: AI32751; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Early stages of T cell development are thought to include a series of coordinated interactions between thymocytes and other cells of the thymus. A monoclonal **antibody** specific for mouse CD81 was identified that blocked the appearance of alpha beta but not gamma delta T cells in fetal organ cultures initiated with day 14.5 thymus lobes. In reaggregation cultures with CD81-transfected fibroblasts, CD4-CD8- thymocytes differentiated into CD4+CD8+ T cells. Thus, interactions between immature thymocytes and stromal cells expressing CD81 are required and may be sufficient to induce early events associated with T cell development.

4/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08698811 96042117 PMID: 7595190
Engaging CD19 or target of an antiproliferative **antibody** 1 on human B lymphocytes induces binding of B cells to the interfollicular stroma of human tonsils via integrin alpha 4/beta 1 and fibronectin.
Behr S; Schriever F
Department of Hematology and Oncology, Virchow University Hospital, Humboldt University Berlin, Germany.
Journal of experimental medicine (UNITED STATES) Nov 1 **1995**, 182 (5) p1191-9, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Adhesion of B lymphocytes within the different compartments of secondary lymphoid organs is essential for the function of the humoral immune response. It is not currently known how the temporary immobilization of B cells in distinct areas of this complex microenvironment is regulated. The present study aimed at defining B cell antigens that initiate binding of B cells to human tonsil sections in situ. Engaging the B cell antigens CD19 and target of an antiproliferative **antibody** 1 (**TAPA**-1) with monoclonal **antibodies** induced adhesion of these B cells to the interfollicular stroma. This binding occurred through the integrin alpha 4 beta 1 on the B cell surface and via the extracellular matrix protein fibronectin expressed in the interfollicular compartment of the tonsil. Signaling through either antigen, CD19 or **TAPA** -1, depended on tyrosine kinases. Binding induced by engaging CD19 required an intact cytoskeleton, whereas **TAPA**-1-transmitted adhesion did not. We suggest that CD19 and **TAPA**-1 have a novel and unique function by regulating an alpha 4 beta 1/fibronectin-mediated binding of B cells to the interfollicular stroma of lymphoid tissues.

4/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08671423 96011883 PMID: 7589142
Epstein-Barr virus/C3d receptor (CR2, CD21) activated by its extracellular ligands regulates pp105 phosphorylation through two distinct pathways.
Bouillie S; Barel M; Drane P; Cassinat B; Balbo M; Holers V M; Frade R
Immunochimie des Regulations Cellulaires et des Interactions Virales, INSERM U.354, Centre INSERM, Hopital Saint-Antoine, Paris, France.
European journal of immunology (GERMANY) Sep **1995**, 25 (9) p2661-7, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We previously demonstrated that human C3d or pep16, a 16-amino acid synthetic peptide derived from human C3d, induced in vivo and in vitro tyrosine phosphorylation of pp105, an intracellular component found only in human cells that express CR2 at their surface. To determine the contribution of CR2 molecules to this enzymatic regulation, we first analyzed whether activation of CR2 by other extracellular CR2 ligands could trigger such regulation in cell extracts. Subsequently, we used cell extracts of either CR2-positive cells depleted in CR2 molecules by absorption with anti-CR2 **antibodies** or CR2-negative cells transfected with CR2 cDNA. We demonstrate here that pp105 phosphorylation was induced when CR2 was activated by C3d and pep16 as well as by gp350, the Epstein-Barr virus capsid protein or OKB7, an anti-CR2 monoclonal **antibody** (mAb). HB5, another anti-CR2 mAb, which did not activate B lymphocytes through CR2, did not induce pp105 phosphorylation. Thus, C3d, pep16, gp350, and OKB7 presented similar properties in activating CR2 to trigger pp105 phosphorylation and in regulating B lymphocyte proliferation, while HB-5 had no effect on either assays. Furthermore, our data demonstrate that the presence of CR2 activated by its extracellular ligands regulates pp105 phosphorylation through two distinct pathways: one which also requires the presence of non-activated CD19, and one which is independent of CD19. The involvement of CD19 in the first pathway was not due to the formation of putative CR2-CD19 complexes. Both pathways were **TAPA** -1 independent. This is the first demonstration that activated CR2 molecules can play a regulatory role in enzymatic function, such as phosphorylation, despite the absence of CD19 and **TAPA**-1.

4/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08567472 95325577 PMID: 7602090
CD82, member of the tetra-span-transmembrane protein family, is a costimulatory protein for T cell activation.
Lebel-Binay S; Lagaudriere C; Fradelizi D; Conjeaud H
Immunomodulation and Autoimmunity Laboratory, Rene Descartes University, Cochin Hospital, Paris, France.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jul 1 **1995**, 155 (1) p101-10, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is now well documented that full activation of T cells requires a two-signal triggering that can be mimicked, in the absence of accessory cells, by co-immobilization of mAbs directed to stimulatory/accessory molecules (CD2, CD3, CD28, adhesion molecules, etc.). In this report, we describe that engagement of CD82 can delivery such a costimulatory signal for full activation of the human T cell line Jurkat, leading to strong IL-2

production and cell differentiation. The CD82 Ag, which belongs to the new tetra-span-transmembrane family (CD9, CD37, CD53, CD63, and CD81 (**TAPA** -1)), has been identified originally in our laboratory for its enhanced expression on three LAK-susceptible cell lines, and has been characterized as an activation/differentiation marker of mononuclear cells. Jurkat cells, stimulated in vitro by co-immobilization of anti-CD82 and anti-CD3 mAbs, produced high levels of IL-2, became strongly adherent to plastic dishes, and developed dendritic processes. These morphologic changes, associated with a total arrest of cell proliferation, were not the result of cell death but rather of cell differentiation, as shown by an increase in their metabolic activity. Costimulation through both CD82 and CD3 induced up-regulation of both IL-2 and IFN-gamma mRNA synthesis (but not of IL-4) and an increased expression of HLA class I molecules at the cell surface, which was inhibited by anti-IFN-gamma Ab.

4/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08554452 95310806 PMID: 7790779
CD82, tetra-span-transmembrane protein, is a regulated transducing molecule on U937 monocytic cell line.
Lebel-Binay S; Lagaudriere C; Fradelizi D; Conjeaud H
Laboratoire d'Immunomodulation et Autoimmunite, Institut National de la Sante et de la Recherche Medicale, Hopital Cochin, Paris, France.
Journal of leukocyte biology (UNITED STATES) Jun **1995**, 57 (6) p956-63, ISSN 0741-5400 Journal Code: 8405628
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mononuclear cell surface protein IA4, recently classified as CD82, was originally identified in our laboratory by the IA4 monoclonal **antibody** (mAb), because of its high expression on three lymphoblastoid, LAK-susceptible, variant cell lines. We have characterized CD82 as a new activation/differentiation marker of mononuclear cells. This protein belongs to the new family of TST proteins (tetra spans transmembrane), which includes CD9, CD37, CD53, CD63, and CD81 (**TAPA** -1). Here we demonstrate that cross-linking of IA4 mAbs induces an increase of intracellular free calcium in U937 cells and tyrosine phosphorylation of various proteins. Our data indicate that the intracellular calcium increase is initiated by a phospholipase C (PLC)-induced PtdIns(1,4,5)P3 second messenger followed by a more stable change, linked to extracellular calcium entry. This transducing signal was dependent on dual engagement of both CD82 and Fc receptors. Surface cross-linking of CD82 together with Fc receptors (FcRs) induces a specific long-lasting increase of intracellular calcium, whereas FcR cross-linking alone induces only a transient calcium mobilization. These results suggest that, upon cross-linking of CD82, a multimolecular complex including CD82 and FcR could be induced that is able to trigger signal transduction. We have previously shown that CD82 membrane expression is up-regulated during differentiation of human monocytes. Using U937 cells, we demonstrate here that several cytokines [interleukin-1 beta (IL-1 beta), IL-4, IL-6, IL-13, interferon-gamma, tumor necrosis factor alpha] could significantly up-regulate the surface expression of CD82 antigen, by contrast with FcR surface expression, which was up-regulated only after IFN-gamma treatments. Based on our finding of a strict dependence of CD82 activation on FcR stimulation, we suggest a putative role of CD82 in enhancing FcR-mediated activation of cells from the monocyte/macrophage lineage.

4/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08218327 94355900 PMID: 8075582
New CD from the B cell section of the Fifth International Workshop on Human Leukocyte Differentiation Antigens.
Engel P; Tedder T F
Department of Immunology, Duke University Medical Center, Durham, NC 27710.
Leukemia & lymphoma (SWITZERLAND) **1994**, 13 Suppl 1 p61-4, ISSN 1042-8194 Journal Code: 9007422
Contract/Grant No.: AI-26872; AI; NIAID; CA-34183; CA; NCI; CA-54464; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This review summaries the expression and the molecular and biochemical characteristics of eight new Clusters of Differentiation (CD79-CD86) established by the B cell Section during the Fifth International Workshop on Human Leukocyte Differentiation Antigens. CD79 monoclonal **antibodies** (mAb) identify the mb1 (CD79 alpha) and B29 (CD79 beta) components of the surface immunoglobulin (Ig) receptor complex. CD80 (B7/BB-1) is a costimulatory molecule that serves as the ligand for two molecules expressed on T lymphocytes, CD28 and CTLA-4. CD81 (**TAPA**-1) and CD82 (R2) are new members of the tetra-spans family of transmembrane proteins, which include CD9, CD37, CD53 and CD63. These proteins are postulated to be involved in signal transduction. CD83 (HB15) is a marker for human interdigitating reticulum cells, circulating dendritic cells and Langerhans cells. CDw84 and CD85 are new B cell-associated molecules that are also expressed by monocytes. CD86 is a new B cell activation antigen.

4/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08033012 94164694 PMID: 8119731
Association of four antigens of the tetraspans family (CD37, CD53, **TAPA**-1, and R2/C33) with MHC class II glycoproteins.
Angelisova P; Hilgert I; Horejsi V
Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Praha.
Immunogenetics (UNITED STATES) **1994**, 39 (4) p249-56, ISSN 0093-7711 Journal Code: 0420404
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Four of the tetraspans family antigens expressed in B cells, CD37, CD53, **TAPA**-1, and R2/C33, as well as at least two other molecules, CD19 and CD21, coprecipitate with DR antigens from mild detergent lysates of human B-cell lines and tonsillar B cells. Coprecipitation and preclearing experiments indicate the existence of large multicomponent complexes containing jointly the seven components, although some "incomplete" complexes lacking some of the components may also exist. The complexes contain only a relatively small fraction of the total cellular pool of relevant molecules. The existence of these "tetraspans-DR complexes" may be related to the previously reported antiproliferative and signaling effects of **antibodies** against most of their components.

4/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07930195 94065201 PMID: 8245480
C33 antigen and M38 antigen recognized by monoclonal **antibodies** inhibitory to syncytium formation by human T cell leukemia virus type 1 are

both members of the transmembrane 4 superfamily and associate with each other and with CD4 or CD8 in T cells.

Imai T; Yoshie O

Shionogi Institute for Medical Science, Osaka, Japan.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Dec 1 **1993**, 151 (11) p6470-81, ISSN 0022-1767 Journal Code: 2985117R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

C33 Ag and M38 Ag had been identified by mAb inhibitory to HTLV-1-induced syncytium formation. The cDNA encoding C33 Ag had revealed that it belongs to the newly defined transmembrane 4 superfamily (TM4SF). M38 Ag was detected on virtually all human cell lines and fresh leukocytes except for most granulocytes. It was also expressed on a mouse hybrid cell clone containing human chromosome 11q23-pter. Immunoprecipitation and immunoblot analyses identified a monomeric 26-kDa protein. The M38 epitope was dependent on S-S bonding. These characteristics were very similar to those reported for **TAPA**-1 (the target of antiproliferative **antibody** -1), which also belongs to TM4SF as C33 Ag. We therefore cloned the cDNA of human **TAPA** -1 and expressed it in COS cells. M38 indeed reacted with COS cells expressing human **TAPA** -1. We concluded that M38 Ag was identical to **TAPA**-1. To further investigate the biologic functions of C33 Ag and M38 Ag (**TAPA** -1) and their roles in HTLV-1-induced syncytium formation, molecules associated with these Ag were examined in T cells. Immunoprecipitation from surface-iodinated cell lysates revealed that proteins co-precipitated by C33 and M38 were mostly common including each other. Sequential immunoprecipitation-immunoblot experiments confirmed that C33 Ag and M38 Ag (**TAPA**-1) were associated with each other. The association was further confirmed in BHK cells doubly transfected with human cDNA for C33 Ag and **TAPA**-1. We extended similar analyses and found that C33 Ag and M38 Ag (**TAPA**-1) were regularly associated with CD4 or CD8. The association of these Ag on the cell surface was further supported by co-modulation of M38 Ag (**TAPA**-1), CD4 and CD8 with C33 Ag. This is the first time that a physical association between the members of TM4SF is demonstrated. Furthermore, the regular association of C33 Ag and M38 Ag (**TAPA**-1) with CD4 or CD8 might indicate that they play a role in expression and/or function of the CD4/CD8 co-receptor complex.

4/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07876603 94014351 PMID: 8409388

The **TAPA** -1 molecule is associated on the surface of B cells with HLA-DR molecules.

Schick M R; Levy S

Department of Medicine, Stanford University Medical Center, CA 94305-5306.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Oct 15 **1993**, 151 (8) p4090-7, ISSN 0022-1767 Journal Code: 2985117R

Contract/Grant No.: CA34233; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

TAPA -1 is a transmembrane protein that has been shown to be involved in cell growth and cellular adhesion. Our studies were aimed at determining the mechanisms of the biologic phenomena mediated by **TAPA** -1, which include the identification of proteins that are associated with it on the surface of lymphocytes. We and others have previously shown that Leu-13, a leukocyte Ag, is one such molecule and that in B cells **TAPA** -1 is associated with the CD19 Ag. Herein we identify an additional molecule, HLA-DR, that is noncovalently associated on the surface of B

cells with **TAPA** -1. This association was first detected by immunoprecipitation by anti-**TAPA**-1 and by anti-HLA-DR **antibodies** in the presence of mild detergents. The initial observation was confirmed by 2-dimensional SDS-PAGE and by direct identification of **TAPA**-1 in anti-HLA-DR immunoprecipitates by Western blot analysis. The association of the two molecules on the surface of a human B cell line was shown by cocapping experiments. In addition, **antibodies** to both molecules can induce cellular adhesion and an antiproliferative effect. Because the tissue distribution of these two molecules only partially overlaps, with **TAPA**-1 being expressed on most cell types and MHC class II expressed on a more restricted group of tissue, it is possible that the **TAPA**-1 molecule provides a basic function that can augment a cell type specific activity. In B cells the association of **TAPA** -1 with CD19 and HLA-DR may increase cellular interaction and play a supporting role in the transmission of specific signals.

4/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07815370 93346737 PMID: 7688390
Anti-**TAPA**-1 **antibodies** induce protein tyrosine phosphorylation that is prevented by increasing intracellular thiol levels.
Schick M R; Nguyen V Q; Levy S
Department of Medicine, School of Medicine, Stanford University, CA 94305.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Aug 15 **1993**, 151 (4) p1918-25, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI-07290; AI; NIAID; CA 34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We studied the signal induced by the anti-**TAPA**-1 **antibody** and compared it to the signal induced by anti-IgM **antibodies** in a human B cell line, OCl-LY8. We found that exposure of these cells to either **antibody** resulted in a rapid increase in protein tyrosine phosphorylation which was prevented by inhibitors of tyrosine kinases. Tyrosine phosphorylation was an early event in the cascase leading to the antiproliferative effect of the anti-**TAPA**-1 **antibody**. However, 2-ME, a reducing agent that is not an inhibitor of tyrosine kinases, prevented both tyrosine phosphorylation and the antiproliferative effect of the **antibody** . Cells grown in low concentrations of 2-ME did not exhibit an increase in tyrosine phosphorylation in response to the anti-**TAPA**-1 **antibody** and were insensitive to the antiproliferative effect of the **antibody** . In contrast, the same cells maintained in 2-ME were able to induce tyrosine phosphorylation in response to anti-IgM. The use of 2-ME resulted in an increase in intracellular thiols, mostly glutathione. Moreover, compounds that block glutathione synthesis rendered cells susceptible to the **antibody** , even in the presence of 2-ME. These experiments demonstrate that tyrosine kinases are involved in propagating the antiproliferative signal initiated by the anti-**TAPA**-1 **antibody** and suggest that this signal is dependent upon the level of intracellular thiols.

4/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07717627 93239379 PMID: 8478146
Expression of the neuroglandular antigen and analogues in melanoma. CD9 expression appears inversely related to metastatic potential of melanoma.
Si Z; Hersey P

Immunology and Oncology Unit, Mater Misericordiae Hospital, Newcastle, NSW, Australia.
International journal of cancer. Journal international du cancer (UNITED STATES) Apr 22 **1993**, 54 (1) p37-43, ISSN 0020-7136
Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Immunohistological methods were used to examine the relation between the metastatic potential of melanoma and expression of the neuroglandular antigen (CD63) and other members of this family of molecules, CD53, CD37, CD9 and the target of an anti-proliferative **antibody** (**TAPA**-I), as well as MHC-class-I and -II antigens. The criteria used to establish metastatic potential were their relation to thickness of the primary melanoma, and differences in expression between vertical and radial growth phases of primary melanoma and between primary and metastatic melanoma. Studies on basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC) were also included as controls for malignant skin cancers with low metastatic potential. Expression of CD9 and MHC-class-I antigen was found to be inversely related to thickness of the primary tumor, and CD9 was expressed predominantly on primary rather than on metastatic tumors. CD9 expression correlated with MHC-class-I expression on melanoma, and both were expressed on BCCs and SCCs having low metastatic potential, but not on compound nevi. CD63 and **TAPA**-I were expressed on nevi but not on SCC and BCC. Leu 13 is a molecule associated with **TAPA**-I in lymphomas, and was found to be expressed in sections from 5 out of 34 primary and 5 out of 21 metastatic melanoma. CD53 and CD37 were not detected on melanoma. Our results indicate that several members of the neuroglandular antigen are expressed in melanoma and that low expression of CD9 on primary melanomas might have prognostic significance with respect to the potential for metastasis.

4/3,AB/72 (Item 72 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07569233 93094596 PMID: 1281197
T and B cell epitope mapping of SM23, an integral membrane protein of Schistosoma mansoni.
Reynolds S R; Shoemaker C B; Harn D A
Department of Tropical Public Health, Harvard School of Public Health, Boston, MA 02115.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Dec 15 **1992**, 149 (12) p3995-4001, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI24557; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

SM23 is an integral membrane protein of the blood-vessel dwelling parasitic worm Schistosoma mansoni. This protein has been detected with **antibodies** in all stages of the parasite found in the human host, notably the lung stage, and therefore is of interest as a vaccine candidate. In addition SM23 has been shown to be a member of a proposed new superfamily of membrane proteins whose structures do not conform to the previously known classifications. To date there are 13 members including ME491 (CD63, Pltgp40), CD9 (p23), **TAPA**-1, CD37, CD53, MRC OX-44, CO-029, MRP-1, L6, the gene product of TI-1, the target of mAb AD-1, SM23, and SJ23 (the Schistosoma japonicum homologue). Most of these molecules except for those in the two blood vessel-dwelling parasites are found in membranes of hemopoietic and/or malignant cells and all have unknown function. In this study we used recombinantly expressed full-length and

partial molecules as well as synthesized peptides to map T cell and B cell epitopes of SM23. The two predicted external hydrophilic domains were found to be highly immunogenic and contained several B cell epitopes. There were at least four T cell epitopes in the large hydrophilic domain. One segment of 23 amino acids contained both a T cell and B cell epitope as well as the putative glycosylation site. This particular segment was recognized by immune sera and cells of every mouse strain tested. The elucidation of these epitopes demonstrates the immunogenic nature of this molecule and raises questions as to the role of SM23 in the host/parasite relationship.

4/3,AB/73 (Item 73 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07490058 93017900 PMID: 1401919
C33 antigen recognized by monoclonal **antibodies** inhibitory to human T cell leukemia virus type 1-induced syncytium formation is a member of a new family of transmembrane proteins including CD9, CD37, CD53, and CD63.
Imai T; Fukudome K; Takagi S; Nagira M; Furuse M; Fukuhara N; Nishimura M ; Hinuma Y; Yoshie O
Shionogi Institute for Medical Science, Osaka, Japan.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Nov 1 **1992**, 149 (9) p2879-86, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
C33 Ag was originally identified by mAb inhibitory to syncytium formation induced by human T cell leukemia virus type 1. The Ag was shown to be a highly heterogeneous glycoprotein consisting of a 28-kDa protein and N-linked oligosaccharides ranging from 10 to 50 kDa. In the present study, cDNA clones were isolated from a human T cell cDNA expression library in Escherichia coli by using mAb C33. The identity of cDNA was verified by immunostaining and immunoprecipitation of transfected NIH3T3 cells with mAb. The cDNA contained an open reading frame of a 267-amino acid sequence which was a type III integral membrane protein of 29.6 kDa with four putative transmembrane domains and three putative N-glycosylation sites. The C33 gene was found to belong to a newly defined family of genes for membrane proteins, such as CD9, CD37, CD53, CD63, and **TAPA**-1, and was identical to R2, a cDNA recently isolated because of its strong up-regulation after T cell activation. Availability of mAb for C33 Ag enabled us to define its distribution in human leukocytes. C33 Ag was expressed in CD4+ T cells, CD19+ B cells, CD14+ monocytes, and CD16+ granulocytes. Its expression was low in CD8+ T cells and mostly negative in CD16+ NK cells. PHA stimulation enhanced the expression of C33 Ag in CD4+ T cells by about 5-fold and in CD8+ T cells by about 20-fold. PHA stimulation also induced the dramatic size changes in the N-linked sugars previously shown to accompany human T cell leukemia virus type 1-induced transformation of CD4+ T cells.

4/3,AB/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07490053 93017895 PMID: 1383329
The CD19/CD21 signal transducing complex of human B lymphocytes includes the target of antiproliferative **antibody**-1 and Leu-13 molecules.
Bradbury L E; Kansas G S; Levy S; Evans R L; Tedder T F
Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston, MA 02115-6084.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Nov 1 **1992**, 149 (9) p2841-50, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI-26872; AI; NIAID; CA-34183; CA; NCI; CA-54464; CA; NCI; +

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

CD19 is a member of the Ig superfamily expressed on the surface of B lymphocytes that may be involved in the regulation of B cell function. Immunoprecipitation studies with B cell lines solubilized by digitonin have shown CD19 to be part of a multimolecular complex that includes CD21 (CR2) and other unidentified proteins. In this study, two of the CD19-associated proteins were identified as **TAPA**-1, which is expressed on most cell types, and Leu-13, which is expressed on subsets of lymphoid cells. **TAPA** -1 and Leu-13 are physically associated in many cell lineages. CD19 and CD21 mAb each specifically coprecipitated proteins of the same size as those precipitated by **TAPA**-1 and Leu-13 mAb from B cell lines and cDNA-transfected K562 cell lines. Western blot analysis with a **TAPA**-1 mAb verified the identity of **TAPA**-1 in CD19 and CD21 immunoprecipitated materials. In addition, when **TAPA**-1 or Leu-13 were crosslinked and patched on the cell surface, all of the CD19 comigrated with **TAPA**-1 and some of the CD19 comigrated with Leu-13. Furthermore, mAb binding to CD19, CD21, **TAPA**-1, and Leu-13 on B cell lines induced similar biologic responses, including the induction of homotypic adhesion, inhibition of proliferation, and an augmentation of the increase in intracellular [Ca2+] induced by suboptimal cross-linking of surface Ig on B cell lines. Together, these data suggest that **TAPA**-1 and Leu-13 are broadly expressed members of a signal transduction complex in which lineage-specific proteins, such as CD19 and CD21, provide cell-specific functions.

4/3,AB/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07310433 92242909 PMID: 1573270

A member of the tetra spans transmembrane protein superfamily is recognized by a monoclonal **antibody** raised against an HLA class I-deficient, lymphokine-activated killer-susceptible, B lymphocyte line. Cloning and preliminary functional studies.

Gil M L; Vita N; Lebel-Binay S; Miloux B; Chalon P; Kaghad M; Marchiol-Fournigault C; Conjeaud H; Caput D; Ferrara P; et al

UA1156 Centre National de la Recherche Scientifique, Institut Gustave Roussy, Villejuif, France.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) May 1 **1992**, 148 (9) p2826-33, ISSN 0022-1767 Journal Code: 2985117R

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The IA4 mAb was identified among a series of **antibodies** raised in BALB/c mice after immunization against a HLA class I-deficient, lymphokine-activated killer (LAK)-susceptible EBV-B lymphocyte line. The IA4 **antibody** was selected because of its high expression, in the range of 10(5) to 25 x 10(5) sites/cell, on several B lymphocyte lines (EBV-transformed or Burkitt) and monocytic lines such as HL60 and U937, and because its expression was correlated with both target susceptibility to LAK lysis and reduced expression of HLA class I surface Ag on two pairs of EBV-B-transformed cell lines (721/721.134 and MM/10F2). Despite the strategy followed to raise the mAb and the correlation mentioned above, no direct role of the IA4 molecules in LAK susceptibility has been established, since the IA4 molecule is poorly expressed on the sensitive targets Daudi and K562; moreover, the IA4 **antibody** did not affect reproducibly the in vitro killing of positive target cells by LAK effectors. The IA4 **antibody** was poorly immunoprecipitating and the surface molecule recognized was identified by gene cloning following an expression strategy using a U937 cDNA library transfected in COS cells, and

a screening strategy based on membrane expression of IA4 molecule. The IA4 cDNA is virtually identical to "R2," a mRNA species previously identified in activated human T cells by subtractive hybridization. The IA4 cDNA contains an open reading frame coding for a protein 267 amino acids long with four potential transmembrane domains and one large external hydrophilic domain of about 110 amino acids, possibly glycosylated. The encoded protein belongs to a family of surface molecules, the tetra spans transmembrane protein superfamily, all displaying the four transmembrane domains, expressed on various cell types including lymphocytes (CD9, CD37, CD53, **TAPA**-1), melanoma cells (ME491), and intestinal cells (CO-029). These molecules have been reported to be involved in cell activation and cell death. Surprisingly, the Schistosoma mansoni Ag Sm23 displays significant homologies with this family. The IA4 molecule is a widely distributed surface marker expressed on circulating lymphocytes and monocytes, newborn thymocytes, and the cell lines mentioned above. The IA4 molecule expression is up-regulated upon cell activation. Weakly expressed on resting peripheral T and B lymphocytes and large granular lymphocytes (NK), its expression roughly doubles after activation by PHA, staphylococcus aureus Cowan I, and IL-2, respectively.(ABSTRACT TRUNCATED AT 400 WORDS)

4/3,AB/76 (Item 76 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07245899 92167302 PMID: 1371549

ME491 melanoma-associated glycoprotein family: antigenic identity of ME491, NKI/C-3, neuroglandular antigen (NGA), and CD63 proteins.

Demetrick D J; Herlyn D; Tretiak M; Creasey D; Clevers H; Donoso L A; Vennegoor C J; Dixon W T; Jerry L M

Oncology Research Group, Faculty of Medicine, University of Calgary, Alberta, Canada.

Journal of the National Cancer Institute (UNITED STATES) Mar 18 **1992**, 84 (6) p422-9, ISSN 0027-8874 Journal Code: 7503089

Contract/Grant No.: CA-10815; CA; NCI; CA-25874; CA; NCI

Erratum in J Natl Cancer Inst 1992 May 6;84(9) 727

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Numerous monoclonal **antibodies** (MAbs) have been produced to antigens found in human melanomas. Three of the best characterized melanoma antigens include the melanoma-associated glycoproteins (MAGs) defined by two reagent families--the ME491 family (including ME491, 8-1H, and 8-2A) and the NKI/C-3 family (including NKI/C-3 and NKI/black-13)--as well as the neuroglandular antigen (NGA) defined by MAbs LS59, LS62, and LS140. These three antigens have significant similarities in tissue distribution, biosynthesis, and structure. The ME491 MAG has been cloned, mapped, and sequenced. Numerous non-melanoma-associated proteins (Sm23, CO-029, R2, **TAPA**-1, CD9, CD37, CD53, and CD63) have recently been shown to have significant homology to this sequence. PURPOSE: We conducted this study to investigate the similarity between the two MAG antigens and NGA. METHODS: Several reagents defining the three different melanoma antigens were compared, using competition immunoprecipitation, immunoassay, and inhibition radioimmunoassay techniques. RESULTS: Immunoassay experiments show that MAbs defining the three melanoma antigens bind to affinity-purified ME491 antigen and inhibit each other from binding in an inhibition radioimmunoassay. Competition immunoprecipitation experiments demonstrate that the ME491 and NKI/C-3 **antibodies** bind to NGA. Rabbit anti-ME491 idiotype serum recognizes determinants shared by NKI/C-3 and the anti-NGA MAbs. A competition immunoprecipitation experiment also confirms the identity of CD63, as defined by MAb RUU-SP 2.28, with the three melanoma antigens. CONCLUSION: These data indicate that the MAGs defined by ME491

and NKI/C-3 as well as the anti-NGA **antibodies** are epitopes of the same molecule, which is identical to CD63 by both immunochemical and molecular genetic investigations. IMPLICATIONS: Our results indicate that the data obtained in studies of these three melanoma antigens may be pooled, and we propose that the molecule recognized by these reagents be classified as CD63.

4/3,AB/77 (Item 77 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07205708 92140457 PMID: 1779990
Further characterisation of the Schistosoma japonicum protein Sj23, a target antigen of an immunodiagnostic monoclonal **antibody**.
Davern K M; Wright M D; Herrmann V R; Mitchell G F
Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia.
Molecular and biochemical parasitology (NETHERLANDS) Sep **1991**, 48 (1) p67-75, ISSN 0166-6851 Journal Code: 8006324
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sj23, the 23-kDa target antigen in Schistosoma japonicum adult worms of the hybridoma monoclonal **antibody** (mAb) I-134, has been identified and cloned from cDNA libraries, mAb I-134 has been successfully used in immunodiagnostic assays to detect S. japonicum infection in Philippine patients. Sequence analysis has shown that Sj23 is the homologue, with 84% amino acid identity, of Sm23, a 23-kDa molecule from S. mansoni worms previously described from our laboratory. The domain structures of Sj23 and Sm23 are strikingly similar to the human membrane proteins ME491, CD37, CD53 and **TAPA** -1, which may suggest a functional role for the schistosome molecules in cellular proliferation.

4/3,AB/78 (Item 78 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07146316 92078843 PMID: 1720807
Identification of the motility-related protein (MRP-1), recognized by monoclonal **antibody** M31-15, which inhibits cell motility.
Miyake M; Koyama M; Seno M; Ikeyama S
Department of Thoracic Surgery, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan.
Journal of experimental medicine (UNITED STATES) Dec 1 **1991**, 174 (6) p1347-54, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A murine monoclonal **antibody** (M31-15) was identified using the penetration-inhibiting assay of a human lung adenocarcinoma cell line (MAC10) and remarkably inhibited the phagokinetic tract motility of various cancer cell lines. The antigen, motility-related protein (MRP-1), recognized by M31-15, was 25- and 28-kD proteins, and M31-15 was used to isolate a cDNA clone from a human breast carcinoma cDNA library. Sequence analysis revealed that MRP-1 had strong similarity with a B cell surface antigen (CD37), a melanoma-associated antigen (ME491), the target of an antiproliferative **antibody** (**TAPA**-1), a human tumor-associated antigen (CO-029), and the Sm23 antigen of the trematode parasite Schistosoma mansoni.

4/3,AB/79 (Item 79 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07036601 91348240 PMID: 1879540
Novel structurally distinct family of leucocyte surface glycoproteins including CD9, CD37, CD53 and CD63.
Horejsi V; Vlcek C
Institute of Molecular Genetics, Czechoslovak Academy of Sciences, Prague.
FEBS letters (NETHERLANDS) Aug 19 **1991**, 288 (1-2) p1-4, ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several of the recently described leucocyte surface (glyco)-proteins with significant amino acid sequence similarity (human CD9, CD37, CD53, CD63, **TAPA** -1, CO-029 and R2 and several homologues of other species) are distinguished by the polypeptide chain apparently four times crossing the membrane. Although the biological role of none of these molecules is known, their structure, associations with other membrane components and the effects of specific monoclonal **antibodies** suggest that they may constitute a family of ion channels or other transport molecules.

4/3,AB/80 (Item 80 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07006991 91318144 PMID: 1650385
Genomic organization and chromosomal localization of the **TAPA**-1 gene.
Andria M L; Hsieh C L; Oren R; Francke U; Levy S
Department of Medicine/Oncology, Stanford University School of Medicine, CA.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Aug 1 **1991**, 147 (3) p1030-6, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI07290; AI; NIAID; CA34233; CA; NCI; GM26105; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
TAPA -1 is a 26-kDa integral membrane protein expressed on many human cell types. **Antibodies** against **TAPA**-1 induce homotypic aggregation of cells and can inhibit their growth. The murine homologue of **TAPA** -1 was cloned from both cDNA and genomic DNA libraries. A very high level of homology was found between human and mouse **TAPA**-1. The 5' untranslated region of the **TAPA**-1 gene resembles housekeeping gene promoters with respect to G + C content and the presence of potential Sp1 binding sites. The chromosomal localization of human and murine **TAPA** -1 genes was determined by Southern blot experiments using DNA from somatic cell hybrids. The genes were found to be part of a conserved syntenic group in mouse chromosome 7 and the short arm of human chromosome 11. The organization of the **TAPA** -1 gene and the projection of the exon boundaries on the proposed protein structure are presented.

4/3,AB/81 (Item 81 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07006719 91317825 PMID: 1860863
Structure and membrane topology of **TAPA**-1.
Levy S; Nguyen V Q; Andria M L; Takahashi S
Department of Medicine, Stanford University School of Medicine, California 94305.

Journal of biological chemistry (UNITED STATES) Aug 5 **1991**, 266 (22) p14597-602, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: CA34233; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

TAPA-1 (the target of an antiproliferative **antibody**) is a 26-kDa cell surface protein expressed on most human cell lines. **TAPA** -1 is a member of an evolutionarily related family of cell surface proteins all of which contain four transmembrane domains. A model is proposed for topology of **TAPA** -1 based on proteolysis studies in the in vitro translated protein embedded into microsomal membranes. This analysis predicts that the amino and the carboxyl termini of the molecule are cytoplasmic and that the two hydrophilic regions of the molecule are extracellular. The antigenic epitope of the human **TAPA**-1 is contained within a subregion of the second extracellular domain of the protein. This is the only region in the protein that has not been tightly conserved in mammalian evolution.

4/3,AB/82 (Item 82 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06893811 91203909 PMID: 2017181
The rat leukocyte antigen MRC OX-44 is a member of a new family of cell surface proteins which appear to be involved in growth regulation.
Bellacosa A; Lazo P A; Bear S E; Tsichlis P N
Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111.
Molecular and cellular biology (UNITED STATES) May **1991**, 11 (5) p2864-72, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: CA-06927; CA; NCI; CA-38047; CA; NCI; RR-05539; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Moloney murine leukemia virus (MoMuLV)-induced rat T-cell lymphomas express discrete 1.8-, 2.2-, and 4-kb mRNA transcripts hybridizing under conditions of reduced stringency to a probe derived from a region upstream of the first exon of the Tpl-1/Ets-1 gene. Screening a cDNA library from one rat T-cell lymphoma with this genomic probe yielded 15 cDNA clones which were derived from 10 different genes. One of these genes, defined by the cDNA clone pRcT7a, was expressed as a 1.8-kb mRNA transcript in spleen and thymus but not in other normal rat tissues. Expression of the gene defined by the pRcT7a cDNA clone in a series of MoMuLV-induced rat T-cell lymphomas showed a perfect correlation with the expression of the rat leukocyte antigen MRC OX-44. Because of this observation, the pRcT7a clone was sequenced and it was shown to identify a gene coding for a 219-amino-acid protein. The homology between pRcT7a and the Tpl-1 probe used for its detection mapped within the 3' untranslated region of the pRcT7a cDNA clone. The pRcT7a protein, which exhibits four putative transmembrane regions and three putative glycosylation sites, contains a region which is nearly identical in sequence to a peptide derived from the rat leukocyte antigen MRC OX-44. This finding suggested that the pRcT7a cDNA clone defines the gene coding for OX-44. To confirm this finding, a pRcT7a construct in the retrovirus vector pZipNeo was introduced into the OX-44- T-cell lymphoma line 2788. Immunostaining with the MRC OX-44 monoclonal **antibody** followed by flow cytometry revealed that following gene transfer, the 2788 cells became OX-44+. Sequence comparisons revealed that pRcT7a/MRC OX-44 is a member of a family of genes which includes the melanoma-specific antigen ME491; the human leukocyte antigen CD37; the protein **TAPA**-1, which is expressed on the surface of human

ells and appears to be involved in growth regulation; the human crointestinal tumor antigen CO-029; and the Schistosoma nsoni-associated antigen Sm23.

4/3,AB/83 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12913693 BIOSIS NO.: 200100120842
Retinal pigment epithelium express CD81 (target of the antiproliferative **antibody**).
AUTHOR: Geisert E E Jr(a); Abel H J; Fan L; Geisert G R
AUTHOR ADDRESS: (a)Univ Of Tennessee Hlth Sci Ctr, Memphis, TN**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7062
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The present study focuses on the role of CD81 (the target of the antiproliferative **antibody**,**TAPA**) in the regulation of the growth of retinal pigment epithelium (RPE). RPE were cultured from eight-day old rat pups. The level of CD81 in the cultures was defined by immunoblot methods and the distribution of the protein was examined using indirect immunohistochemical methods. In addition, the effects of the **antibody** binding were tested in culture. CD81 was found in all layers of the normal retina with a distinct lack of labeling in the inner and outer segments of the photoreceptors. Based on our original immunohistochemical analysis (Clarke and Geisert, 1998 Mol. Vision, http://www.molvis.org/molvis/v4/a3/), it was difficult to determine if CD81 was expressed by RPE. By examining cultures of RPE we demonstrated that CD81 was expressed on the surface of these cells and that it was concentrated at regions of cell-cell contact. When the AMP1 **antibody** (directed against the large extracellular loop of CD81) was added to cultured RPE the mitotic activity of the cells was depressed. Previous studies demonstrated that CD81 was expressed in retinal glia, the Muller cells which span the thickness of the retina, and astrocytes found in the ganglion cell layer. The present study demonstrated that CD81 was also expressed by RPE. The dramatic effects of the AMP1 **antibody** and the location of CD81 at regions of cell-cell contact support the hypothesis that this molecule is part of a molecular switch controlling contact inhibition.

2000

4/3,AB/84 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12869665 BIOSIS NO.: 200100076814
Intraparenchymal infusion of anti-**TAPA**/CD81 **antibodies** leads to functional recovery after spinal cord injury.
AUTHOR: Hamers F P(a); Dijkstra S; Lankhorst A J; Joosten E A; Bar P R; Gispen W H; Geisert E E Jr
AUTHOR ADDRESS: (a)Rudolf Magnus Institute for Neurosciences, University Medical Center, Utrecht**Netherlands
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-18617

2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Modulation of the glial response to spinal cord injury may lead to enhanced functional recovery. The monoclonal **antibody** AMP1 was found to alter the stability of astrocyte-astrocyte contact in vitro and to inhibit proliferation of astrocytes and microglia. Furthermore, the AMP1 antigen (**TAPA**/CD81) is upregulated after traumatic spinal cord injury. Therefore we studied whether intralesional infusion of AMP1-mAb could enhance functional recovery after spinal cord contusion injury. Female Wistar rats were subjected to a moderate spinal cord contusion injury and implanted at the lesion site with a stainless steel cannula connected to an osmotic minipump. Two different doses of AMP1-mAb and one dose of pre-immune IgG were infused for 14 days. Neurological function was regularly assessed on several function tests for 8 weeks. The lower dose of AMP1 led to significantly better function on BBB (+-1.5 point) and Gridwalk tests as compared to the IgG control from 3 weeks onward. Hindpaw fine motor function, as assessed by BBB-subscores, was significantly better from 2 weeks onward. The higher dose of AMP1 did not differ from IgG control. These data suggest that AMP1 might be of value in the treatment of spinal cord injury, either by modulating the primary inflamatory process or by affecting the formation of the glial scar.

2000

4/3,AB/85 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12612456 BIOSIS NO.: 200000365958
The role of **TAPA** (CD81) in microglial activation after spinal cord injury in the rat.
AUTHOR: Dijkstra S(a); Geisert E E Jr; Gispen W H(a); Bar P R(a); Joosten E A J(a)
AUTHOR ADDRESS: (a)Dept. of Experimental Neurology, RMI for Neurosciences, UMC Utrecht, Utrecht**Netherlands
JOURNAL: European Journal of Neuroscience 12 (Supplement 11):p288
2000
MEDIUM: print
CONFERENCE/MEETING: Meeting of the Federation of European Neuroscience Societies Brighton, UK June 24-28, 2000
ISSN: 0953-816X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

4/3,AB/86 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12497517 BIOSIS NO.: 200000251019
RPE express the target of the antiproliferative **antibody** (**TAPA**, CD81).
AUTHOR: Geisert E E(a); Geisert G R(a)

AUTHOR ADDRESS: (a)Anatomy and Neurobiology, Univ Tennessee/Memphis, Memphis, TN**USA
JOURNAL: IOVS 41 (4):pS605 March 15, **2000**
CONFERENCE/MEETING: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA April 30-May 05, 2000
SPONSOR: Association for Research in Vision and Ophthalmology
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

4/3,AB/87 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11919027 BIOSIS NO.: 199900165136
Increased detection of a Glial membrane protein (**TAPA**/CD81) after transient focal ischemia.
AUTHOR: Benhayon David; Geisert Eldon E; Nowak Thaddeus S
AUTHOR ADDRESS: University Tennessee, Memphis, TN**USA
JOURNAL: Stroke 30 (1):p275 Jan., **1999**
CONFERENCE/MEETING: 24th American Heart Association International Conference on Stroke and Cerebral Circulation Nashville, Tennessee, USA February 4-6, 1999
SPONSOR: American Heart Association
ISSN: 0039-2499
RECORD TYPE: Citation
LANGUAGE: English
1999

4/3,AB/88 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11773909 BIOSIS NO.: 199900020018
Regulation glial cell number by **TAPA** (the target of the antiproliferative **antibody**, CD81) in the developing rodent brain and retina.
AUTHOR: Geisert E E Jr(a)
AUTHOR ADDRESS: (a)Dep. Anat. Neurobiol., Univ. Tenn. Coll. Med., Memphis, TN**USA
JOURNAL: Molecular Biology of the Cell 9 (SUPPL.):p228A Nov., **1998**
CONFERENCE/MEETING: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998
SPONSOR: American Society for Cell Biology
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
1998

4/3,AB/89 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11458218 BIOSIS NO.: 199800239550
Expression of the target of the antiproliferative **antibody** (**TAPA**, CD81) in the retina.
AUTHOR: Geisert E E Jr(a); Clarke K(a); Maecker H T; Levy S
AUTHOR ADDRESS: (a)Dep. Anatomy and Neurobiol., Univ. Tennessee Coll. Med., Memphis, TN**USA
JOURNAL: IOVS 39 (4):pS121 March 15, **1998**

CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 10-15, 1998
SPONSOR: Association for Research in Vision and Ophthalmology
RECORD TYPE: Citation
LANGUAGE: English
1998

4/3,AB/90 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10285397 BIOSIS NO.: 199698740315
Characterization of novel complexes on the cell surface between integrins and proteins with 4 transmembrane domains (TM4 proteins).
AUTHOR: Berditchevski Fedor(a); Zutter Mary M; Hemler Martin E(a)
AUTHOR ADDRESS: (a)Dana-Farber Cancer Inst., Rm. M613, 44 Binney St., Boston, MA 02115**USA
JOURNAL: Molecular Biology of the Cell 7 (2):p193-207 **1996**
ISSN: 1059-1524
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Here we identified several new integrin/TM4 protein complexes on the cell surface. By immunoprecipitation stringent conditions, and by reciprocal immunoprecipitation, we found that alpha-3-beta-1 and alpha-6-beta-1 integrins but not alpha-2-beta-1, alpha-5-beta-1, or alpha-6-beta-4 integrins associated with CD9 and CD81 in a alpha-3-beta-1/CD81, alpha-3-beta-1/CD9, alpha-6-beta-1/CD81, and alpha-6-beta-1/CD9 complexes. Also, cross-linking experiments established that a alpha-3-beta-1/CD81, alpha-3-beta-1/CD9, and alpha-3-beta-1/CD63 associations occur on the surface of intact cells and suggested that a critical interaction site is located within extracellular domains. Cross-linking in conjunction with reimmunoprecipitation indicated that larger multi-component alpha-3-beta-1/TM4/TM4 complexes (alpha-3-beta-1/CD9/CD63, alpha-3-beta-1/CD81/CD63, and alpha-3-beta-1/CD9/CD81) also could be detected on the cell surface. Immunofluorescent staining showed redistribution of a alpha-3-beta-1/TM4 complexes toward the periphery of cells plated on various extracellular matrix substrates and also showed that these complexes were localized in cell footprints. Staining of human tissues yielded additional results consistent with co-localization of alpha-3-beta-1 and CD9, CD63, and CD81 proteins. In conclusion we suggest that the prevalence of integrin/TM4 complexes in diverse cellular environments is indicative of their general physiological importance.

1996

4/3,AB/91 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10162735 BIOSIS NO.: 199698617653
Antibodies against CD19 and **TAPA**-1 induce binding of B cells to the interfollicular stroma of human tonsils through integrin alpha-4-beta-1 and fibronectin.
AUTHOR: Behr S; Schriever F
AUTHOR ADDRESS: Univ. Hosp. Virchow, Dep. Hematol. Oncol., Humboldt Univ., Augustenburger Platz 1, 13353 Berlin**Germany
JOURNAL: Onkologie 18 (SUPPL. 2):p190 **1995**
CONFERENCE/MEETING: Annual Congress of the German and Austrian Societies for Hematology and Oncology Hamburg, Germany October 8-11, 1995

ISSN: 0378-584X
RECORD TYPE: Citation
LANGUAGE: English
1995

4/3,AB/92 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09250375 BIOSIS NO.: 199497258745
Expression of Bcl-2 in human B-cell lines does not protect cells from the antiproliferative effect of the anti-**TAPA**-1 **antibodies**.
AUTHOR: Levy S; Nguyen V Q
AUTHOR ADDRESS: Dep. Med., Stanford Univ. Sch. Med., Stanford, CA 94305** USA
JOURNAL: FASEB Journal 8 (4-5):pA217 **1994**
CONFERENCE/MEETING: Experimental Biology 94, Parts I and II Anaheim, California, USA April 24-28, 1994
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English
1994

4/3,AB/93 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09096172 BIOSIS NO.: 199497104542
TAPA-1, a component of the CD19/CD21 complex.
AUTHOR: Bradbury Laura; Tedder Thomas F
AUTHOR ADDRESS: Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA** USA
JOURNAL: Tissue Antigens 42 (4):p323 **1993**
CONFERENCE/MEETING: 5th International Conference on Human Leukocyte Differentiation Antigens Boston, Massachusetts, USA November 3-7, 1993
ISSN: 0001-2815
RECORD TYPE: Citation
LANGUAGE: English
1993

4/3,AB/94 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09096112 BIOSIS NO.: 199497104482
Large noncovalent complexes involving HLA-DR and four antigens of the tetraspans superfamily (CD37, CD53, **TAPA**-1 and R2).
AUTHOR: Angelisova P; Hilgert I; Horejsi V
AUTHOR ADDRESS: Inst. Molecular Genetics, Praha**Czech Republic
JOURNAL: Tissue Antigens 42 (4):p308 **1993**
CONFERENCE/MEETING: 5th International Conference on Human Leukocyte Differentiation Antigens Boston, Massachusetts, USA November 3-7, 1993
ISSN: 0001-2815
RECORD TYPE: Citation
LANGUAGE: English
1993

4/3,AB/95 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08637860 BIOSIS NO.: 199345055935
The CD19-CR2-**TAPA**-1 complex, CD45 and signaling by the antigen receptor of B lymphocytes.
AUTHOR: Fearon Douglas T
AUTHOR ADDRESS: Johns Hopkins Univ. Sch. Med., 1059 Ross, 720 Rutland Ave., Baltimore, MD 21205**USA
JOURNAL: Current Opinion in Immunology 5 (3):p341-348 **1993**
ISSN: 0952-7915
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
1993

4/3,AB/96 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08601827 BIOSIS NO.: 199345019902
Sensitivity of the signal transduced by the anti-**TAPA**-1 mAb to intracellular thiol levels.
AUTHOR: Levy S; Nguyen V G; Schick M R
AUTHOR ADDRESS: Stanford Univ. Sch. Med., Stanford, CA 94305**USA
JOURNAL: Journal of Immunology 150 (8 PART 2):p98A **1993**
CONFERENCE/MEETING: Joint Meeting of the American Association of Immunologists and the Clinical Immunology Society Denver, Colorado, USA May 21-25, 1993
ISSN: 0022-1767
RECORD TYPE: Citation
LANGUAGE: English
1993

10571943 20117181 PMID: 10653456
Hepatitis C--virology and future antiviral targets.
Di Bisceglie A M
Department of Internal Medicine, Saint Louis University School of Medicine, Missouri 63104, USA.
American journal of medicine (UNITED STATES) Dec 27 1999, 107 (6B) p45S-48S, ISSN 0002-9343 Journal Code: 0267200
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hepatitis C virus is a single-stranded RNA virus with a genome approximately 9,000 nucleotides in length. The genome consists of a single, large open reading frame (ORF) and 5' and 3' untranslated regions. The highly conserved 5' untranslated region is 341 nucleotides in length with a complex secondary structure and may function as an internal ribosomal entry site (IRES). The 3' untranslated region is approximately 500 nucleotides in length and contains a hypervariable region, followed by a poly(U) sequence and a highly conserved 98-nucleotide element with a stable secondary structure. The ORF codes form a single polyprotein that is processed into as many as 10 polypeptides, including a capsid protein (core), two envelope proteins (E1 and E2), and nonstructural proteins (NS2, NS3, NS4, and NS5). Potentially suitable antiviral targets include the IRES, protease, helicase, and RNA polymerase. In vitro studies show that **antisense** oligonucleotides can **inhibit** the production of structural HCV proteins and may be therapeutically useful if the problems of stability and delivery can be solved. The binding of HCV envelope proteins to **CD81**, a potential receptor for viral entry into hepatocytes, has recently been described and also raises the possibility of agents to block the binding to **CD81** or the entry of the virus into cells.

3/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10397995 99389749 PMID: 10459022
Role of transmembrane 4 superfamily (TM4SF) proteins CD9 and **CD81** in muscle cell fusion and myotube maintenance.
Tachibana I; Hemler M E
Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of cell biology (UNITED STATES) Aug 23 1999, 146 (4) p893-904, ISSN 0021-9525 Journal Code: 0375356
Contract/Grant No.: GM38903; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The role of transmembrane 4 superfamily (TM4SF) proteins during muscle cell fusion has not been investigated previously. Here we show that the appearance of TM4SF protein, CD9, and the formation of CD9-beta1 integrin complexes were both regulated in coordination with murine C2C12 myoblast cell differentiation. Also, anti-CD9 and anti-**CD81** monoclonal **antibodies** substantially **inhibited** and delayed conversion of C2C12 cells to elongated myotubes, without affecting muscle-specific protein expression. Studies of the human myoblast-derived RD sarcoma cell line further demonstrated that TM4SF proteins have a role during muscle cell fusion. Ectopic expression of CD9 caused a four- to eightfold increase in RD cell syncytia formation, whereas anti-CD9 and anti-**CD81** **antibodies** markedly delayed RD syncytia formation. Finally, anti-CD9 and anti-**CD81** monoclonal **antibodies** triggered apoptotic degeneration of C2C12 cell myotubes after they were formed. In summary, TM4SF proteins such as CD9 and **CD81** appear to promote muscle cell

expressed by keratinocytes clearly delineating filopodia at lateral and apical surfaces. CD63 and CD151 are largely expressed in the intracellular compartment, although some membrane expression is observed. We found accumulation of CD9, **CD81**, and CD151 together with alpha3 and beta1 integrins at intercellular junctions. In low calcium medium, this intercellular space is crossed by a zipper of filopodia enriched in alpha3beta1 and tetraspanin proteins. Interestingly, the expression of CD9, **CD81** , and beta1 and alpha3 integrins was detected in the footprints and rippings of motile keratinocytes, suggesting their role in both adhesion to extracellular matrix and keratinocyte motility. beta1 integrins were only partially activated in the rips, whereas cytoskeleton-linking proteins such as talin were completely absent. On the other hand, antitetraspanin **antibodies** did not stain focal adhesions, which contain talin. The involvement of tetraspanins in keratinocyte motility was assessed in a wound healing migration assay. **Inhibition** of cell migration was observed with **antibodies** to CD9, **CD81**, beta1, and alpha3, and, to a lesser extent, to CD151. Together these results indicate that tetraspanin-integrin complexes might be involved in transient adhesion and integrin recycling during keratinocyte migration, as well as in intercellular recognition.

3/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10740031 20267869 PMID: 10806098
Transmembrane-4-superfamily proteins CD151 and **CD81** associate with alpha 3 beta 1 integrin, and selectively contribute to alpha 3 beta 1-dependent neurite outgrowth.
Stipp C S; Hemler M E
Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute and Department of Pathology, Harvard Medical School, Boston, MA 02115, USA.
Journal of cell science (ENGLAND) Jun 2000, 113 (Pt 11) p1871-82, ISSN 0021-9533 Journal Code: 0052457
Contract/Grant No.: GM38903; GM; NIGMS; NS10344; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Proteins in the transmembrane-4-superfamily (TM4SF) form many different complexes with proteins in the integrin family, but the functional utility of these complexes has not yet been demonstrated. Here we show that TM4SF proteins CD151, **CD81** , and CD63 co-distribute with alpha3beta1 integrin on neurites and growth cones of human NT2N cells. Also, stable CD151-alpha3beta1 and **CD81** -alpha3beta1 complexes were recovered in NT2N detergent lysates. Total NT2N neurite outgrowth on laminin-5 (a ligand for alpha3beta1 integrin) was strongly **inhibited** by anti-CD151 and -**CD81** **antibodies** either together (approximately 85% **inhibition**) or alone (approximately 45% **inhibition**). Notably, these **antibodies** had no **inhibitory** effect on NT2N neurites formed on laminin-1 or fibronectin, when alpha3beta1integrin was not engaged. Neurite number, length, and rate of extension were all affected by anti-TM4SF **antibodies**. In summary: (1) these substrate-dependent **inhibition** results strongly suggest that CD151 and **CD81** associations with alpha3beta1 are functionally relevant, (2) TM4SF proteins CD151 and **CD81** make a strong positive contribution toward neurite number, length, and rate of outgrowth, and (3) NT2N cells, a well-established model of immature central nervous system neurons, can be a powerful system for studies of integrin function in neurite outgrowth and growth cone motility.

3/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

0036-8075 Journal Code: 0404511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Chronic hepatitis C virus (HCV) infection occurs in about 3 percent of the world's population and is a major cause of liver disease. HCV infection is also associated with cryoglobulinemia, a B lymphocyte proliferative disorder. Virus tropism is controversial, and the mechanisms of cell entry remain unknown. The HCV envelope protein E2 binds human **CD81**, a tetraspanin expressed on various cell types including hepatocytes and B lymphocytes. Binding of E2 was mapped to the major extracellular loop of **CD81**. Recombinant molecules containing this loop bound HCV and **antibodies** that neutralize HCV infection in vivo **inhibited** virus binding to **CD81** in vitro.

3/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09807389 98234412 PMID: 9566977

Regulation of endothelial cell motility by complexes of tetraspan molecules **CD81** /TAPA-1 and CD151/PETA-3 with alpha3 beta1 integrin localized at endothelial lateral junctions.

Yanez-Mo M; Alfranca A; Cabanas C; Marazuela M; Tejedor R; Ursa M A; Ashman L K; de Landazuri M O; Sanchez-Madrid F

Servicio de Inmunologia, Hospital de la Princesa, Universidad Autonoma de Madrid.

Journal of cell biology (UNITED STATES) May 4 1998, 141 (3) p791-804 , ISSN 0021-9525 Journal Code: 0375356
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Cell-to-cell junction structures play a key role in cell growth rate control and cell polarization. In endothelial cells (EC), these structures are also involved in regulation of vascular permeability and leukocyte extravasation. To identify novel components in EC intercellular junctions, mAbs against these cells were produced and selected using a morphological screening by immunofluorescence microscopy. Two novel mAbs, LIA1/1 and VJ1/16, specifically recognized a 25-kD protein that was selectively localized at cell-cell junctions of EC, both in the primary formation of cell monolayers and when EC reorganized in the process of wound healing. This antigen corresponded to the recently cloned platelet-endothelial tetraspan antigen CD151/PETA-3 (platelet-endothelial tetraspan antigen-3), and was consistently detected at EC cell-cell contact sites. In addition to CD151/PETA-3, two other members of the tetraspan superfamily, CD9 and **CD81**/ TAPA-1 (target of antiproliferative **antibody** -1), localized at endothelial cell-to-cell junctions. Biochemical analysis demonstrated molecular associations among tetraspan molecules themselves and those of CD151/ PETA-3 and CD9 with alpha3 beta1 integrin. Interestingly, mAbs directed to both CD151/PETA-3 and **CD81**/ TAPA-1 as well as mAb specific for alpha3 integrin, were able to **inhibit** the migration of ECs in the process of wound healing. The engagement of CD151/PETA-3 and **CD81**/TAPA-1 **inhibited** the movement of individual ECs, as determined by quantitative time-lapse video microscopy studies. Furthermore, mAbs against the CD151/PETA-3 molecule diminished the rate of EC invasion into collagen gels. In addition, these mAbs were able to increase the adhesion of EC to extracellular matrix proteins. Together these results indicate that **CD81**/TAPA-1 and CD151/PETA-3 tetraspan molecules are components of the endothelial lateral junctions implicated in the regulation of cell motility, either directly or by modulation of the function of the associated integrin heterodimers.

3/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09766049 98189267 PMID: 9514697
Functional analysis of four tetraspans, CD9, CD53, **CD81**, and CD82, suggests a common role in costimulation, cell adhesion, and migration: only CD9 upregulates HB-EGF activity.
Lagaudriere-Gesbert C; Le Naour F; Lebel-Binay S; Billard M; Lemichez E; Boquet P; Boucheix C; Conjeaud H; Rubinstein E
INSERM U283, Hopital Cochin, Paris, France.
Cellular immunology (UNITED STATES) Dec 15 1997, 182 (2) p105-12, ISSN 0008-8749 Journal Code: 1246405
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Molecules of the tetraspan superfamily are engaged in multimolecular complexes containing other proteins such as beta 1 integrins and MHC antigens. Although their functions are not clear, they have been suggested to play a role in cell adhesion and migration, signal transduction, and costimulation. We have in this paper directly compared the functional properties of four tetraspans, CD9, CD53, **CD81**, and CD82. mAbs to any of these molecules were able to deliver a costimulatory signal for CD3-mediated activation of the T cell line Jurkat. CD82 mAbs were the most efficient in triggering this effect. Moreover, engagement of CD9, **CD81**, and CD82 induced the homotypic aggregation of the megakaryocytic cell line HEL, and **inhibited** the migration of this cell line. Similar results were obtained with the preB cell line NALM-6 using the CD9 and **CD81** mAbs. The **CD81** mAb 5A6 produced the strongest effects. Therefore, the tetraspans are recognized by mAbs which produce similar effects on the same cell lines. This is consistent with the tetraspans being included in large molecular complexes and possibly forming a tetraspan network (the tetraspan web). We also demonstrate that the tetraspans are likely to keep specific functional properties inside this network. Indeed, we have demonstrated that the human CD9 is able, like the monkey molecule, to upregulate the activity of the transmembrane precursor of heparin-binding EGF as a receptor for the diphtheria toxin when cotransfected in murine LM cells. Neither **CD81**, nor CD82 had such activity. By using chimeric CD9/**CD81** molecules we demonstrate that this activity requires the second half of CD9, which contains the large extracellular loop, the fourth transmembrane region, and the last short cytoplasmic domain.

3/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09594139 98028160 PMID: 9362067
Integrin alpha 6A beta 1 induces **CD81**-dependent cell motility without engaging the extracellular matrix migration substrate.
Domanico S Z; Pelletier A J; Havran W L; Quaranta V
Department of Cell Biology, Scripps Research Institute, La Jolla, California 92037, USA.
Molecular biology of the cell (UNITED STATES) Nov 1997, 8 (11) p2253-65, ISSN 1059-1524 Journal Code: 9201390
Contract/Grant No.: CA-47858; CA; NCI; DE-10063; DE; NIDCR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is well established that integrins and extracellular matrix (ECM) play key roles in cell migration, but the underlying mechanisms are poorly defined. We describe a novel mechanism whereby the integrin alpha 6 beta 1,

DIALOG(R)File 155:MEDLINE(R)

09274047 97160557 PMID: 9006891
A novel link between integrins, transmembrane-4 superfamily proteins (CD63 and **CD81**), and phosphatidylinositol 4-kinase.
Berditchevski F; Tolias K F; Wong K; Carpenter C L; Hemler M E
Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of biological chemistry (UNITED STATES) Jan 31 1997, 272 (5) p2595-8, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: GM38903; GM; NIGMS; GM54387; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Enzymatic and immunochemical assays show a phosphatidylinositol 4-kinase in novel and specific complexes with proteins (CD63 and **CD81**) of the transmembrane 4 superfamily (TM4SF) and an integrin (alpha3beta1). The size (55 kDa) and other properties of the phosphatidylinositol 4-kinase (PI 4-K) (stimulated by nonionic detergent, **inhibited** by adenosine, **inhibited** by monoclonal **antibody** 4CG5) are consistent with PI 4-K type II. Not only was PI 4-K associated with alpha3beta1-CD63 complexes in alpha3-transfected K562 cells, but also it could be co-purified from CD63 in untransfected K562 cells lacking alpha3beta1. Thus, TM4SF proteins may link PI 4-K activity to the alpha3beta1 integrin. The alpha5beta1 integrin, which does not associate with TM4SF proteins, was not associated with PI 4-K. Notably, alpha3beta1-CD63-**CD81** -PI 4-K complexes are located in focal complexes at the cell periphery rather than in focal adhesions. The novel linkage between integrins, transmembrane 4 proteins, and phosphoinositide signaling at the cell periphery may play a key role in cell motility and provides a signaling pathway distinct from conventional integrin signaling through focal adhesion kinase.

3/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08902813 96249501 PMID: 8668914
Triggering of target of an antiproliferative **antibody**-1 (TAPA-1/**CD81**) up-regulates the release of tumour necrosis factor-alpha by the EBV-B lymphoblastoid cell line JY.
Altomonte M; Montagner R; Pucillo C; Maio M
Advanced Immunotherapy Unit, INRCCS-CRO, Department of Sciences and Biomedical Technologies, University of Udine, Italy.
Scandinavian journal of immunology (ENGLAND) Apr 1996, 43 (4) p367-73, ISSN 0300-9475 Journal Code: 0323767
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Target of an antiproliferative **antibody**-1 (TAPA-1/**CD81**) has been shown to be non-covalently associated to HLA-DR antigens on the cell surface of B cells. In this study the authors report that triggering of **CD81** by MoAb 5A6 or 1D6 significantly ($P < 0.05$) up-regulates the release of tumour necrosis factor-alpha (TNF-alpha) by the Epstein-Barr virus-positive (EBV)-B lymphoblastoid cell line JY. The accumulation of TNF-alpha in the culture medium of JY cells incubated with either anti-**CD81** MoAb was found to be dose-dependent and similar to that obtained following crosslinking of HLA-DR antigens with MoAb L243. The effect of the combination of anti-**CD81** and anti-HLA-DR MoAb on the release of TNF-alpha by JY cells was not synergistic or additive. In addition, the combination of anti-**CD81** and anti-HLA-DR MoAb did not affect proliferation and homotypic aggregation of JY cells induced by each MoAb used alone. Both anti-**CD81** or anti-HLA-DR MoAb induced protein

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         (c) 2002 BIOSIS
*File   5: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

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            6071  RIBOZYM?
         1115505  ANTIBOD?
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 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13533020   22198952   PMID: 12210409
  Cellular glycosaminoglycans and low density lipoprotein receptor are
involved in hepatitis C virus adsorption.
  Germi Raphaele; Crance Jean-Marc; Garin Daniel; Guimet Josette;
Lortat-Jacob Hugues; Ruigrok Rob W H; Zarski Jean-Pierre; Drouet Emmanuel
  Laboratoire de Virologie Moleculaire et Structurale EA 2939, Universite
Joseph Fourier, Faculte de Medecine-Pharmacie de Grenoble, La Tronche,
France.
  Journal of medical virology (United States)  Oct 2002,  68  (2)  p206-15
,  ISSN 0146-6615  Journal Code: 7705876
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  The initial binding of Hepatitis C virus (HCV) to the cell membrane is a
critical determinant of pathogenesis. Two putative HCV receptors have been
identified, CD81 and low-density lipoprotein receptor (LDLr).
CD81 interacts in vitro with the HCV E2 envelope glycoprotein, and
LDLr interacts with HCV present in human plasma. In order to characterize
these potential receptors for HCV, virus from plasma, able to replicate in
cell culture, was inoculated on Vero cells or human hepatocarcinoma cells.
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HCV adsorption was assessed by quantitating cell-associated viral RNA by a real-time RT-PCR method. Anti-LDLr **antibody**, low and very low density lipoproteins **inhibited** significantly HCV adsorption, confirming the role of LDLr as HCV receptor. Only one out of the two anti-**CD81** **antibodies** used in this study led to a partial **inhibition** of HCV binding. This study also highlights a role for glycosaminoglycans (GAGs) in HCV adsorption: treatment of virus with heparin led to 70% **inhibition** of attachment, as did desulfation of cellular GAGs. Treatment of Vero cells with heparin-lyase significantly **inhibited** virus attachment but by only 30%. These results demonstrate the complexity of the HCV binding step in which LDLr interacts strongly with HCV, whereas the interaction of HCV with GAGs and particularly with **CD81** seem to be more moderate. J. Med. Virol. 68:206-215, 2002. Copyright 2002 Wiley-Liss, Inc.

3/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13519529 22174922 PMID: 12186916
Interaction of hepatitis C virus-like particles and cells: a model system for studying viral binding and entry.
Triyatni Miriam; Saunier Bertrand; Maruvada Padma; Davis Anthony R; Ulianich Luca; Heller Theo; Patel Arvind; Kohn Leonard D; Liang T Jake
Liver Diseases Section, National Institute of Diabetes and DigestiveKidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
Journal of virology (United States) Sep 2002, 76 (18) p9335-44,
ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Hepatitis C virus-like particles (HCV-LPs) containing the structural proteins of HCV H77 strain (1a genotype) was used as a model for HCV virion to study virus-cell interaction. HCV-LPs showed a buoyant density of 1.17 to 1.22 g/cm(3) in a sucrose gradient and formed double-shelled particles 35 to 49 nm in diameter. Flow cytometry analysis by an indirect method (detection with anti-E2 **antibody**) and a direct method (use of dye-labeled HCV-LPs) showed that HCV-LPs binds to several human hepatic (primary hepatocytes, HepG2, HuH7, and NKNT-3) and T-cell (Molt-4) lines. HCV-LPs binding to cells occurred in a dose- and calcium-dependent manner and was not mediated by **CD81**. Scatchard plot analysis suggests the presence of two binding sites for HCV-LPs with high (K(d) approximately 1 microg/ml) and low (K(d) approximately 50 to 60 microg/ml) affinities of binding. Anti-E1 and -E2 **antibodies inhibited** HCV-LPs binding to cells. While preincubation of HCV-LPs with very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), or high-density lipoprotein (HDL) blocked its binding to cells, preincubation of cells with VLDL, LDL, HDL, or anti-LDL-R **antibody** did not. Confocal microscopy analysis showed that, after binding to cells, dye-labeled HCV-LPs were internalized into the cytoplasm. This process could be **inhibited** with anti-E1 or anti-E2 **antibodies** , suggesting that E1 and E2 proteins mediate HCV-LPs binding and, subsequently, their entry into cells. Altogether, our results indicate that HCV-LPs can be used to further characterize the mechanisms involved in the early steps of HCV infection.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13466148 22166746 PMID: 12175627
Expression of transmembrane 4 superfamily (TM4SF) proteins and their role in hepatic stellate cell motility and wound healing migration.

Mazzocca Antonio; Carloni Vinicio; Sciammetta Silvia; Cordella Claudia; Pantaleo Pietro; Caldini Anna; Gentilini Paolo; Pinzani Massimo
Dipartimento di Medicina Interna, Universita degli Studi di Firenze, Viale Morgagni, 85, I-50134, Florence, Italy
Journal of hepatology (England) Sep 2002, 37 (3) p322, ISSN 0168-8278 Journal Code: 8503886
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
BACKGROUND/AIMS: Migration of activated hepatic stellate cells (HSC) is a key event in the progression of liver fibrosis. Little is known about transmembrane proteins involved in HSC motility. Tetraspanins (TM4SF) have been implicated in cell development, differentiation, motility and tumor cell invasion. We evaluated the expression and function of four TM4SF, namely CD9, **CD81** , CD63 and CD151, and their involvement in HSC migration, adhesion, and proliferation.METHODS/RESULTS: All TM4SF investigated were highly expressed at the human HSC surface with different patterns of intracellular distribution. Monoclonal **antibodies** directed against the four TM4SF **inhibited** HSC migration induced by extracellular matrix proteins in both wound healing and haptotaxis assays. This **inhibition** was independent of the ECM substrates employed (collagen type I or IV, laminin), and was comparable to that obtained by incubating the cells with an anti-beta1 blocking mAb. Importantly, cell adhesion was unaffected by the incubation with the same **antibodies**. Co-immunoprecipitation studies revealed different patterns of association between the four TM4SF studied and beta1 integrin. Finally, anti-TM4SF **antibodies** did not affect HSC growth.CONCLUSIONS: These findings provide the first characterization of tetraspanins expression and of their role in HSC migration, a key event in liver tissue wound healing and fibrogenesis.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13038578 21881750 PMID: 11884446
Complement receptor type 1 (CD35) mediates **inhibitory** signals in human B lymphocytes.
Jozsi Mihaly; Prechl Jozsef; Bajtay Zsuzsa; Erdei Anna
Department of Immunology and Research Group of the Hungarian Academy of Sciences, Eotvos Lorand University, Budapest, Hungary.
Journal of immunology (Baltimore, Md. : 1950) (United States) Mar 15 2002, 168 (6) p2782-8, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The complement system---particularly component C3---has been demonstrated to be a key link between innate and adaptive immunity. The trimolecular complex of complement receptor type 2 (CR2), CD19, and **CD81** is known to promote B cell activation when coligated with the B cell Ag receptor. In the present study, we aimed to elucidate the role of human complement receptor type 1 (CR1), the other C3-receptor on B cells. As ligand, aggregated C3 and aggregated C3(H(2)O), i.e., multimeric "C3b-like C3", are used, which bind to CR1, but not to CR2. In experiments studying the functional consequences of CR1-clustering, the multimeric ligand is shown to **inhibit** the proliferation of tonsil B cells activated with a suboptimal dose of anti-IgM F(ab')(2). Importantly, this **inhibitory** activity also occurs in the presence of the costimulatory cytokines IL-2 and IL-15. The anti-IgM-induced transient increase in the concentration of intracellular free Ca(2+) and phosphorylation of several cytoplasmic proteins are strongly reduced in the presence of the CR1 ligand. Data presented indicate that CR1 has a negative regulatory role in the B cell Ag

receptor mediated activation of human B lymphocytes.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12982348 21663975 PMID: 11805154
Murine CD9 is the receptor for pregnancy-specific glycoprotein 17.
Waterhouse Roseann; Ha Cam; Dveksler Gabriela S
Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814-4799, USA.
Journal of experimental medicine (United States) Jan 21 2002, 195 (2) p277-82, ISSN 0022-1007 Journal Code: 2985109R
Contract/Grant No.: HD35832; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Pregnancy-specific glycoproteins (PSGs) are a family of highly similar secreted proteins produced by the placenta. PSG homologs have been identified in primates and rodents. Members of the human and murine PSG family induce secretion of antiinflammatory cytokines in mononuclear phagocytes. For the purpose of cloning the receptor, we screened a RAW 264.7 cell cDNA expression library. The PSG17 receptor was identified as the tetraspanin, CD9. We confirmed binding of PSG17 to CD9 by ELISA, flow cytometry, alkaline phosphatase binding assays, and in situ rosetting. Anti-CD9 monoclonal **antibody inhibited** binding of PSG17 to CD9-transfected cells and RAW 264.7 cells. Moreover, PSG17 binding to macrophages from CD9-deficient mice was significantly reduced. We then tested whether PSG17 binds to other members of the murine tetraspanin family. PSG17 did not bind to cells transfected with CD53, CD63, **CD81**, CD82, or CD151, suggesting that PSG17-CD9 binding is a specific interaction. We have identified the first receptor for a murine PSG as well as the first natural ligand for a member of the tetraspanin superfamily.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12852339 21663948 PMID: 11805134
Primary hepatocytes of Tupaia belangeri as a potential model for hepatitis C virus infection.
Zhao Xiping; Tang Zhen-Ya; Klumpp Bettina; Wolff-Vorbeck Guido; Barth Heidi; Levy Shoshana; von Weizsacker Fritz; Blum Hubert E; Baumert Thomas F
Department of Medicine II, University of Freiburg, Freiburg, Germany.
Journal of clinical investigation (United States) Jan 2002, 109 (2) p221-32, ISSN 0021-9738 Journal Code: 7802877
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) is a major cause of chronic hepatitis worldwide, but the study of HCV infection has been hampered by the lack of an in vitro or in vivo small animal model. The tree shrew Tupaia belangeri is susceptible to infection with a variety of human viruses in vivo, including hepatitis viruses. We show that primary Tupaia hepatocytes can be infected with serum- or plasma-derived HCV from infected humans, as measured by de novo synthesis of HCV RNA, analysis of viral quasispecies evolution, and detection of viral proteins. Production of infectious virus could be demonstrated by passage to naive hepatocytes. To assess whether viral entry in Tupaia hepatocytes was dependent on the recently isolated HCV E2 binding protein **CD81**, we identified and characterized Tupaia **CD81**. Sequence analysis of cloned Tupaia cDNA revealed a high degree of homology between Tupaia and human **CD81** large extracellular loops (LEL).

Cellular binding of E2 and HCV infection could not be **inhibited** by anti-**CD81 antibodies** or soluble **CD81**-LEL, suggesting that viral entry can occur through receptors other than **CD81**. Thus, primary Tupaia hepatocytes provide a potential model for the study of HCV infection of hepatocytes.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12832614 21827605 PMID: 11838967
Comparison of adhesion mechanisms and surface protein expression in CD77-positive and CD77-negative Burkitt's lymphoma cells.
Jackson T; Van Exel C; Reagans K; Verret R; Maloney M
Department of Biology, Spelman College, Atlanta, Georgia 30314-4399, USA.
Cellular and molecular biology (Noisy-le-Grand, France) (France) Nov 2001, 47 (7) p1195-200, ISSN 0145-5680 Journal Code: 9216789
Contract/Grant No.: GM08241; GM; NIGMS; RR11598; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The Burkitt lymphoma-derived Daudi cell line is often used as an in vitro model for germinal center B-cell function. Globotriaosyl ceramide (CD77), a marker for germinal center B-cells, is present on Daudi cells but is deficient in the Daudi-derived mutant VT500 cell line. Previous results showed a correlation in these cells between CD77 expression and expression of the B-cell protein CD19 and indicated that CD19/CD77 interaction is a mechanism for B-cell adhesion. Roles for CD77 in IFN-alpha-induced growth **inhibition** and anti-viral activity also have been described previously. Through flow cytometric analysis and adhesion assays, we investigated whether expression of CD77 was required for cell adhesion pathways induced by IFN or **antibodies** against additional B-cell surface molecules: CD20, CD22, CD38, CD40, **CD81** and HLA-D proteins. In contrast to the pronounced homotypic adhesion induced by treatment with interferon-alpha in Daudi cells, no increase in adhesion was observed in IFN-treated VT500 cells. Of the B-cell proteins tested, only CD22-mediated adhesion and surface expression was stronger in Daudi than in VT500 cells. These results indicate that CD77 may be required for IFN and CD22-associated adhesion pathways, but CD77 is not a universal component of adhesion pathways in these cells.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12831100 21635497 PMID: 11773394
Binding of hepatitis C virus-like particles derived from infectious clone H77C to defined human cell lines.
Wellnitz Sabine; Klumpp Bettina; Barth Heidi; Ito Susumu; Depla Erik; Dubuisson Jean; Blum Hubert E; Baumert Thomas F
Department of Medicine II, University of Freiburg, Freiburg, Germany.
Journal of virology (United States) Feb 2002, 76 (3) p1181-93, ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) is a leading cause of chronic hepatitis in the world. The study of viral entry and infection has been hampered by the inability to efficiently propagate the virus in cultured cells and the lack of a small-animal model. Recent studies have shown that in insect cells, the HCV structural proteins assemble into HCV-like particles (HCV-LPs) with morphological, biophysical, and antigenic properties similar to those of

putative virions isolated from HCV-infected humans. In this study, we used HCV-LPs derived from infectious clone H77C as a tool to examine virus-cell interactions. The binding of partially purified particles to human cell lines was analyzed by fluorescence-activated cell sorting with defined monoclonal **antibodies** to envelope glycoprotein E2. HCV-LPs demonstrated dose-dependent and saturable binding to defined human lymphoma and hepatoma cell lines but not to mouse cell lines. Binding could be **inhibited** by monoclonal anti-E2 **antibodies**, indicating that the HCV-LP-cell interaction was mediated by envelope glycoprotein E2. Binding appeared to be **CD81** independent and did not correlate with low-density lipoprotein receptor expression. Heat denaturation of HCV-LPs drastically reduced binding, indicating that the interaction of HCV-LPs with target cells was dependent on the proper conformation of the particles. In conclusion, our data demonstrate that insect cell-derived HCV-LPs bind specifically to defined human cell lines. Since the envelope proteins of HCV-LPs are presumably presented in a virion-like conformation, the binding of HCV-LPs to target cells may allow the study of virus-host cell interactions, including the isolation of HCV receptor candidates and **antibody**-mediated neutralization of binding.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12795471 21640531 PMID: 11781364
Binding of the hepatitis C virus envelope protein E2 to **CD81** **inhibits** natural killer cell functions.
Tseng Chien-Te K; Klimpel Gary R
Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX 77555, USA.
Journal of experimental medicine (United States) Jan 7 2002, 195 (1) p43-9, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Little is known about how this virus is able to persist or whether this persistence might be because of its ability to alter the early innate immune response. The major HCV envelope protein E2 has been shown to bind to **CD81**. Thus, HCV binding to natural killer (NK) cells could result in the cross-linking of **CD81**. To explore this possibility, we investigated whether cross-linking **CD81** on NK cells could alter NK cell function. **CD81** cross-linking by monoclonal **antibody** (mAb) specific for **CD81** or by immobilized E2 have been shown to result in costimulatory signals for human T cells. In this study, we show that **CD81** cross-linking via immobilized E2 or mAbs specific for **CD81** **inhibits** not only non major histocompatibility complex-restricted cytotoxicity mediated by NK cells but also interferon (IFN)-gamma production by NK cells after exposure to interleukin (IL)-2, IL-12, IL-15, or CD16 cross-linking. These results show that **CD81** cross-linking mediates completely different signals in NK cells versus T cells. Importantly, these results suggest that one mechanism whereby HCV can alter host defenses and innate immunity is via the early **inhibition** of IFN-gamma production by NK cells.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12795470 21640530 PMID: 11781363
Inhibition of natural killer cells through engagement of **CD81** by the major hepatitis C virus envelope protein.
Crotta Stefania; Stilla Annalisa; Wack Andreas; D'Andrea Annalisa; Nuti

Sandra; D'Oro Ugo; Mosca Marta; Filliponi Franco; Brunetto R Maurizia; Bonino Ferruccio; Abrignani Sergio; Valiante Nicholas M
IRIS, Department of Immunology, Chiron S.p.A., 53100 Siena, Italy.
Journal of experimental medicine (United States) Jan 7 2002, 195 (1) p35-41, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The immune response against hepatitis C virus (HCV) is rarely effective at clearing the virus, resulting in approximately 170 million chronic HCV infections worldwide. Here we report that ligation of an HCV receptor (**CD81**) **inhibits** natural killer (NK) cells. Cross-linking of **CD81** by the major envelope protein of HCV (HCV-E2) or anti-**CD81** **antibodies** blocks NK cell activation, cytokine production, cytotoxic granule release, and proliferation. This **inhibitory** effect was observed using both activated and resting NK cells. Conversely, on NK-like T cell clones, including those expressing NK cell **inhibitory** receptors, **CD81** ligation delivered a costimulatory signal. Engagement of **CD81** on NK cells blocks tyrosine phosphorylation through a mechanism which is distinct from the negative signaling pathways associated with NK cell **inhibitory** receptors for major histocompatibility complex class I. These results implicate HCV-E2-mediated **inhibition** of NK cells as an efficient HCV evasion strategy targeting the early antiviral activities of NK cells and allowing the virus to establish itself as a chronic infection.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12779521 21634773 PMID: 11773042
Retinal pigment epithelium of the rat express **CD81**, the target of the anti-proliferative **antibody** (TAPA).
Geisert Eldon E; Abel Haley J; Fan Liying; Geisert Grace R
Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee 38163, USA. egeisert@nb.utmem.edu
Investigative ophthalmology & visual science (United States) Jan 2002, 43 (1) p274-80, ISSN 0146-0404 Journal Code: 7703701
Contract/Grant No.: P30 EY13080; EY; NEI; R01 EY12369; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

PURPOSE: The present study focuses on the role of **CD81**, the target of the anti-proliferative **antibody** (TAPA), in the regulation of the growth of retinal pigment epithelium (RPE). METHODS: RPE of 8-day-old rat pups was cultured. The level of **CD81** in the cultures was defined by immunoblot methods, and the distribution of the protein was examined using indirect immunohistochemical methods. In addition, the effects of the **antibody** binding were tested in culture. RESULTS: **CD81** was found in all layers of the normal retina with a distinct absence of labeling in the inner and outer segments of the photoreceptors. Based on the authors' original immunohistochemical analysis, it was difficult to determine whether **CD81** was expressed by RPE. By examining cultures of RPE it was demonstrated that **CD81** was expressed on the surface of these cells and that it was concentrated at regions of cell-cell contact. Indirect immunohistochemical methods using a peroxidase-labeled secondary **antibody** in albino mice revealed heavy labeling of the RPE in the intact eye. When the AMP1 **antibody** (directed against the large extracellular loop of **CD81**) was added to cultured RPE, the mitotic activity of the cells was depressed. CONCLUSIONS: **CD81** was found in the normal rat retina. Previous studies demonstrated that **CD81** was expressed in retinal glia, the Muller cells that span the thickness of the

retina, and astrocytes found in the ganglion cell layer. The present study demonstrated that **CD81** was also expressed by RPE. The dramatic effects of the AMP1 **antibody** and the location of **CD81** at regions of cell-cell contact support the hypothesis that this molecule is part of a molecular switch controlling contact **inhibition**.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12714599 21599742 PMID: 11739177
Regulatory role of tetraspanin CD9 in tumor-endothelial cell interaction during transendothelial invasion of melanoma cells.
Longo N; Yanez-Mo M; Mittelbrunn M; de la Rosa G; Munoz M L; Sanchez-Madrid F; Sanchez-Mateos P
Servicio de Inmunologia, Hospital General Universitario Gregorio Maranon, Madrid, Spain.
Blood (United States) Dec 15 2001, 98 (13) p3717-26, ISSN 0006-4971 Journal Code: 7603509
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Heterotypic interaction among tumor cells (TCs) and endothelial cells (ECs) may play a critical role during the vascular dissemination of neoplastic cells and during pathologic angiogenesis in tumors. To identify molecules involved in these processes, the distribution of vascular junctional proteins was first studied by immunofluorescence at sites of heterologous intercellular contact using TC-EC mosaic monolayers grown on 2-dimensional collagen. Several members of the tetraspanin superfamily, including CD9, **CD81**, and CD151, were found to localize at the TC-EC contact area. The localization of tetraspanins to the TC-EC heterologous contact area was also observed during the active transmigration of TCs across EC monolayers grown onto 3-dimensional collagen matrices. Dynamic studies by time-lapse immunofluorescence confocal microscopy showed an active redistribution of endothelial CD9 to points of melanoma insertion. Anti-CD9 monoclonal **antibodies** were found to specifically **inhibit** the transendothelial migration of melanoma cells; the **inhibitory** effect was likely caused by a strengthening of CD9-mediated heterotypic interactions of TCs to the EC monolayer. These data support a novel mechanism of tetraspanin-mediated regulation of TC transcellular migration independent of TC motility and growth during metastasis and a role for these molecules in the formation of TC-EC mosaic monolayers during tumor angiogenesis.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12568696 21471950 PMID: 11588022
The dynamics of hepatitis C virus binding to platelets and 2 mononuclear cell lines.
Hamaia S; Li C; Allain J P
Division of Transfusion Medicine, Department of Haematology, University of Cambridge, Cambridge, United Kingdom.
Blood (United States) Oct 15 2001, 98 (8) p2293-300, ISSN 0006-4971 Journal Code: 7603509
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hepatitis C virus (HCV) binds to platelets in chronically infected patients where free HCV constitutes only about 5% of total circulating virus. Free HCV preferentially binds to human mononuclear cell lines but

free and complexed virus binds equally to platelets. The extent of free HCV binding to human Molt-4 T cells (which express **CD81**) and to human promonocytic U937 cells or to platelets (which do not express **CD81**) was similar. The binding of free HCV to the cell lines was saturated at a virus dose of 1 IU HCV RNA per cell but binding to platelets was not saturable. Human anti-HCV IgG, but not anti-**CD81**, markedly **inhibited** HCV binding to target cells in a dose-dependent manner. Human **antibodies** to HCV hypervariable region 1 of E2 glycoprotein partially **inhibited** viral binding to target cells. Recombinant E2 also **inhibited** viral binding to target cells in a dose-dependent manner, with the efficacy of this decreasing in the rank order of Molt-4 cells more than U937 cells more than platelets. In contrast to HCV, recombinant E2 bound to Molt-4 cells to an extent markedly greater than that apparent with U937 cells or platelets. These results suggest that the binding of HCV to blood cells is mediated by multiple cell surface receptors and that recombinant E2 binding may not be representative of the interaction of the intact virus with target cells.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11305829 21351041 PMID: 11457993
Functional analysis of hepatitis C virus E2 glycoproteins and virus-like particles reveals structural dissimilarities between different forms of E2.
Owsianka A; Clayton R F; Loomis-Price L D; McKeating J A; Patel A H
MRC Virology Unit, Institute of Virology, Church Street, Glasgow G11 5JR, UK.
Journal of general virology (England) Aug 2001, 82 (Pt 8) p1877-83, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Structure-function analysis of the hepatitis C virus (HCV) envelope glycoproteins, E1 and E2, has been difficult due to the unavailability of HCV virions. Truncated soluble forms of E2 have been used as models to study virus interaction with the putative HCV receptor **CD81**, but they may not fully mimic E2 structures on the virion. Here, we compared the **CD81** -binding characteristics of truncated E2 (E2(660)) and full-length (FL) E1E2 complex expressed in mammalian cells, and of HCV virus-like particles (VLPs) generated in insect cells. All three glycoprotein forms interacted with human **CD81** in an in vitro binding assay, allowing us to test a panel of well-characterized anti-E2 monoclonal **antibodies** (MAbs) for their ability to **inhibit** the glycoprotein-**CD81** interaction. MAbs specific for E2 amino acid (aa) regions 396-407, 412-423 and 528-535 blocked binding to **CD81** of all antigens tested. However, MAbs specific for regions 432-443, 436-443 and 436-447 **inhibited** the interaction of VLPs, but not of E2(660) or the FL E1E2 complex with **CD81**, indicating the existence of structural differences amongst the E2 forms. These findings underscore the need to carefully select an appropriate ligand for structure-function analysis.

3/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11178752 21191851 PMID: 11294888
Sequence-specific interaction between the disintegrin domain of mouse ADAM 3 and murine eggs: role of beta1 integrin-associated proteins CD9, **CD81**, and CD98.
Takahashi Y; Bigler D; Ito Y; White J M
Department of Cell Biology, University of Virginia Health System, School of Medicine, Charlottesville, Virginia 22908, USA.

Molecular biology of the cell (United States) Apr 2001, 12 (4) p809-20, ISSN 1059-1524 Journal Code: 9201390
Contract/Grant No.: GM-48739; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

ADAM 3 is a sperm surface glycoprotein that has been implicated in sperm-egg adhesion. Because little is known about the adhesive activity of ADAMs, we investigated the interaction of ADAM 3 disintegrin domains, made in bacteria and in insect cells, with murine eggs. Both recombinant proteins **inhibited** sperm-egg binding and fusion with potencies similar to that which we recently reported for the ADAM 2 disintegrin domain. Alanine scanning mutagenesis revealed a critical importance for the glutamine at position 7 of the disintegrin loop. Fluorescent beads coated with the ADAM 3 disintegrin domain bound to the egg surface. Bead binding was **inhibited** by an authentic, but not by a scrambled, peptide analog of the disintegrin loop. Bead binding was also **inhibited** by the function-blocking anti-alpha6 monoclonal **antibody** (mAb) GoH3, but not by a nonfunction blocking anti-alpha6 mAb, or by mAbs against either the alphav or beta3 integrin subunits. We also present evidence that in addition to the tetraspanin CD9, two other beta1-integrin-associated proteins, the tetraspanin **CD81** as well as the single pass transmembrane protein CD98 are expressed on murine eggs. **Antibodies** to CD9 and CD98 **inhibited** in vitro fertilization and binding of the ADAM 3 disintegrin domain. Our findings are discussed in terms of the involvement of multiple sperm ADAMs and multiple egg beta1 integrin-associated proteins in sperm-egg binding and fusion. We propose that an egg surface "tetraspan web" facilitates fertilization and that it may do so by fostering ADAM-integrin interactions.

3/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11160115 21179883 PMID: 11282207
Immunogenicity of the E1E2 proteins of hepatitis C virus expressed by recombinant adenoviruses.
Seong Y R; Choi S; Lim J S; Lee C H; Lee C K; Im D S
Cell Biology Laboratory, Korea Research Institute of Bioscience and Biotechnology, Yusong PO Box 115, Taejon 305-600, South Korea.
Vaccine (England) Apr 6 2001, 19 (20-22) p2955-64, ISSN 0264-410X Journal Code: 8406899
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The E1 and E2 proteins of hepatitis C virus (HCV) are believed to be the viral envelope glycoproteins that are major candidate antigens for HCV vaccine development. We reported previously that the replication-competent recombinant adenovirus encoding core-E1-E2 genes of HCV (Ad/HCV) produces serologically reactive E1 and E2 proteins forming a heterodimer in substantial amounts. Here, we examined immunogenicity of the E1E2 proteins copurified from HeLa cells infected with Ad/HCV virus in mice. Furthermore, we constructed a replication-defective recombinant adenovirus encoding the core-E1-E2 genes of HCV (Ad.CMV.HCV) and examined immunogenicity of the virus in mice. The mice immunized intraperitoneally with the copurified E1E2 proteins induced mainly **antibodies** to E2, but not to E1 by Western blot analysis. The sera of mice immunized with the E1E2 **inhibited** the binding of E2 protein to the major extracellular loop of human **CD81**. E2-specific cytotoxic T cells (CTLs), but not **antibodies** to the E1E2 antigens were induced in the mice intramuscularly immunized with Ad.CMV.HCV virus. When immunized with both Ad.CMV.HCV virus and the E1E2, mice elicited E2-specific CTLs and

antibodies to the E1E2 antigens. The results suggest that immunization of Ad.CMV.HCV virus combined with E2 protein is an effective modality to induce humoral as well as cellular immune response to E2 antigen.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10938445 20499063 PMID: 11044085
Human monoclonal **antibodies** that **inhibit** binding of hepatitis C virus E2 protein to **CD81** and recognize conserved conformational epitopes.
Hadlock K G; Lanford R E; Perkins S; Rowe J; Yang Q; Levy S; Pileri P; Abrignani S; Foung S K
Departments of Pathology, Stanford University, Stanford, CA 94304, USA.
Journal of virology (UNITED STATES) Nov 2000, 74 (22) p10407-16, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: AI40035; AI; NIAID; DA-06596; DA; NIDA; HL-33811; HL; NHLBI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The intrinsic variability of hepatitis C virus (HCV) envelope proteins E1 and E2 complicates the identification of protective **antibodies**. In an attempt to identify **antibodies** to E2 proteins from divergent HCV isolates, we produced HCV E2 recombinant proteins from individuals infected with HCV genotypes 1a, 1b, 2a, and 2b. These proteins were then used to characterize 10 human monoclonal **antibodies** (HMAbs) produced from peripheral B cells isolated from an individual infected with HCV genotype 1b. Nine of the **antibodies** recognize conformational epitopes within HCV E2. Six HMAbs identify epitopes shared among HCV genotypes 1a, 1b, 2a, and 2b. Six, including five broadly reactive HMAbs, could **inhibit** binding of HCV E2 of genotypes 1a, 1b, 2a, and 2b to human **CD81** when E2 and the **antibody** were simultaneously exposed to **CD81**. Surprisingly, all of the **antibodies** that **inhibited** the binding of E2 to **CD81** retained the ability to recognize preformed **CD81**-E2 complexes generated with some of the same recombinant E2 proteins. Two **antibodies** that did not recognize preformed complexes of HCV 1a E2 and **CD81** also **inhibited** binding of HCV 1a virions to **CD81**. Thus, HCV-infected individuals can produce **antibodies** that recognize conserved conformational epitopes and **inhibit** the binding of HCV to **CD81**. The **inhibition** is mediated via **antibody** binding to epitopes outside of the **CD81** binding site in E2, possibly by preventing conformational changes in E2 that are required for **CD81** binding.

3/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10912987 20451111 PMID: 10993933
Recombinant human monoclonal **antibodies** against different conformational epitopes of the E2 envelope glycoprotein of hepatitis C virus that **inhibit** its interaction with **CD81**.
Allander T; Drakenberg K; Beyene A; Rosa D; Abrignani S; Houghton M; Widell A; Grillner L; Persson M A
Karolinska Institute, Department of Medicine and Department of Laboratory Medicine, Center for Molecular Medicine (L8:01), Karolinska Hospital, S-171 76 Stockholm, Sweden.
Journal of general virology (ENGLAND) Oct 2000, 81 Pt 10 p2451-9, ISSN 0022-1317 Journal Code: 0077340
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The **antibody** response to the envelope proteins of hepatitis C virus (HCV) may play an important role in controlling the infection. To allow molecular analyses of protective **antibodies** , we isolated human monoclonal **antibodies** to the E2 envelope glycoprotein of HCV from a combinatorial Fab library established from bone marrow of a chronically HCV-infected patient. Anti-E2 reactive clones were selected using recombinant E2 protein. The bone marrow donor carried HCV genotype 2b, and E2 used for selection was of genotype 1a. The **antibody** clones were expressed as Fab fragments in E. coli, and as Fab fragments and IgG1 in CHO cells. Seven different **antibody** clones were characterized, and shown to have high affinity for E2, genotype 1a. Three clones also had high affinity for E2 of genotype 1b. They all bind to conformation-dependent epitopes. Five clones compete for the same or overlapping binding sites, while two bind to one or two other epitopes of E2. Four clones corresponding to the different epitopes were tested as purified IgG1 for blocking the **CD81**-E2 interaction in vitro; all four were positive at 0.3-0.5 microg/ml. Thus, the present results suggest the existence of at least two conserved epitopes in E2 that mediate **inhibition** of the E2-**CD81** interaction, of which one appeared immunodominant in this donor.

3/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10811107 20351724 PMID: 10891408

Hepatitis C virus glycoprotein E2 binding to **CD81**: the role of E1E2 cleavage and protein glycosylation in bioactivity.

Chan-Fook C; Jiang W R; Clarke B E; Zitzmann N; Maidens C; McKeating J A; Jones I M

NERC Institute of Virology and Environmental Microbiology, Mansfield Road, Oxford, OX1 3SR.

Virology (UNITED STATES) Jul 20 2000, 273 (1) p60-6, ISSN 0042-6822 Journal Code: 0110674

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The hepatitis C virus glycoproteins E1 and 2 have been expressed using recombinant baculoviruses following fusion to the carrier protein glutathione S-transferase (GST). Proteins were expressed singly and as an E1E2 polyprotein with and without an N-terminal affinity tag. Expression of the E1E2 polyprotein, even when preceded by GST, led to processing in insect cells and detection of an E1E2 complex that could be specifically purified by glutathione affinity chromatography. Baculovirus expressed E2 and a purified GST-E1E2 protein bound to the second extracellular loop of **CD81** (EC2), a reported ligand for the molecule, but not to a truncated derivative of **CD81** consisting of only the central domain of the loop. Purified GST-E2, however, failed to bind to **CD81** suggesting a requirement for a free E2 amino terminus for biological activity. The binding to **CD81** by baculovirus expressed E2 protein was comparable to that observed for E2 derived from mammalian cells when detected by a monoclonal **antibody** sensitive to protein conformation. Furthermore, E2 protein expressed in insect cells in the presence of N-butyldeoxynojirimycin, an **inhibitor** of terminal glucose residue processing, formed complexes with E1 and bound to **CD81**-EC2 similarly to untreated protein. Together these data suggest that although hyperglucosylation of E2 does not have a major effect on bioactivity, polyprotein processing to reveal the free amino terminus is required.

3/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806570 20347351 PMID: 10888628

Evaluation of hepatitis C virus glycoprotein E2 for vaccine design: an endoplasmic reticulum-retained recombinant protein is superior to secreted recombinant protein and DNA-based vaccine candidates.

Heile J M; Fong Y L; Rosa D; Berger K; Saletti G; Campagnoli S; Bensi G; Capo S; Coates S; Crawford K; Dong C; Wininger M; Baker G; Cousens L; Chien D; Ng P; Archangel P; Grandi G; Houghton M; Abrignani S

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Journal of virology (UNITED STATES) Aug 2000, 74 (15) p6885-92, ISSN 0022-538X Journal Code: 0113724

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Hepatitis C virus (HCV) is the leading causative agent of blood-borne chronic hepatitis and is the target of intensive vaccine research. The virus genome encodes a number of structural and nonstructural antigens which could be used in a subunit vaccine. The HCV envelope glycoprotein E2 has recently been shown to bind **CD81** on human cells and therefore is a prime candidate for inclusion in any such vaccine. The experiments presented here assessed the optimal form of HCV E2 antigen from the perspective of **antibody** generation. The quality of recombinant E2 protein was evaluated by both the capacity to bind its putative receptor **CD81** on human cells and the ability to elicit **antibodies** that **inhibited** this binding (NOB **antibodies**). We show that truncated E2 proteins expressed in mammalian cells bind with high efficiency to human cells and elicit NOB **antibodies** in guinea pigs only when purified from the core-glycosylated intracellular fraction, whereas the complex-glycosylated secreted fraction does not bind and elicits no NOB **antibodies**. We also show that carbohydrate moieties are not necessary for E2 binding to human cells and that only the monomeric nonaggregated fraction can bind to **CD81** . Moreover, comparing recombinant intracellular E2 protein to several E2-encoding DNA vaccines in mice, we found that protein immunization is superior to DNA in both the quantity and quality of the **antibody** response elicited. Together, our data suggest that to elicit **antibodies** aimed at blocking HCV binding to **CD81** on human cells, the antigen of choice is a mammalian cell-expressed, monomeric E2 protein purified from the intracellular fraction.

3/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10754983 20304866 PMID: 10844555

Tetraspanins are localized at motility-related structures and involved in normal human keratinocyte wound healing migration.

Penas P F; Garcia-Diez A; Sanchez-Madrid F; Yanez-Mo M

Departments of Dermatology and Immunology, Hospital Universitario de La Princesa, Universidad Autonoma de Madrid, Spain. pablofp@hup.es

Journal of investigative dermatology (UNITED STATES) Jun 2000, 114 (6) p1126-35, ISSN 0022-202X Journal Code: 0426720

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have described previously that beta1 integrins, which mediate keratinocyte cell adhesion and migration, are in ligand-occupied conformation at the basal surface but not at the lateral and apical surfaces of keratinocytes. This led us to study the cellular localization and function of tetraspanin molecules, which have been postulated to modulate integrin activity. We found that CD9 and **CD81** are highly

fusion and support myotube maintenance.

3/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10148770 99131987 PMID: 9931299
Transmembrane 4 superfamily protein CD151 (PETA-3) associates with beta 1 and alpha IIb beta 3 integrins in haemopoietic cell lines and modulates cell-cell adhesion.
Fitter S; Sincock P M; Jolliffe C N; Ashman L K
Division of Haematology, Hanson Centre for Cancer Research, Institute of Medical and Veterinary Science, Adelaide, SA, Australia.
Biochemical journal (ENGLAND) Feb 15 1999, 338 (Pt 1) p61-70, ISSN 0264-6021 Journal Code: 2984726R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD151 (PETA-3/SFA-1) is a member of the transmembrane 4 superfamily (TM4SF) of cell-surface proteins and is expressed abundantly both on the cell surface and in intracellular membranes by the haemopoietic cell lines M07e, HEL and K562. In the presence of mild detergent (CHAPS), CD151 co-immunoprecipitated with integrin alpha 4 beta 1, alpha 5 beta 1, alpha 6 beta 1 and alpha IIb beta 3. The association of CD151 with alpha 4 beta 1 and alpha 5 beta 1 seemed to be constitutive, as it was not modified by treatment of M07e cells with cytokines that regulate integrin function by 'inside-out' signalling. CD151 also associated with other tetraspans in an apparently cell-type-specific fashion, as defined by its co-precipitation with CD9, CD63 and **CD81** from M07e cells, but not from K562 cells, which express similar levels of these proteins. F(ab')2 fragments of monoclonal **antibodies** (mAbs) against CD151 caused homotypic adhesion of HEL and K562 cells that was dependent on energy and cytoskeletal integrity and was augmented in the presence of RGDS peptides. The adhesion was not blocked by function-**inhibiting** mAbs against beta 1 or beta 3 integrins, suggesting that cell-cell adhesion was not mediated by the binding of integrin to a cell-associated ligand. Furthermore, mAb CD151 did not affect adhesion of the cells to fibronectin, laminin, collagen or fibrinogen, which are ligands for alpha 4 beta 1, alpha 5 beta 1, alpha 6 beta 1 and alpha IIb beta 3 integrins. Taken together, these results indicate that the ligation of CD151 does not induce the up-regulation of integrin avidity, but might act as a component of integrin signalling complexes.

3/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10092974 99077164 PMID: 9862348
Gamma-glutamyl transpeptidase, an ecto-enzyme regulator of intracellular redox potential, is a component of TM4 signal transduction complexes.
Nichols T C; Guthridge J M; Karp D R; Molina H; Fletcher D R; Holers V M
Department of Medicine, University of Colorado Health Sciences Center, Denver 80262, USA.
European journal of immunology (GERMANY) Dec 1998, 28 (12) p4123-9, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD21 (C3dg/EBV receptor) is physically associated on B cells with a complex of proteins that includes CD19 and the widely distributed tetraspan 4 (TM4) family protein **CD81** as well as other TM4 proteins (CD53, CD37 and CD82). Monoclonal **antibodies** (mAb) were generated that blocked

homotypic adhesion induced by CD21 ligands in the human B cell line Balm-1. One **inhibitory** mAb (3A8) was found to recognize the ecto-enzyme gamma-glutamyl transpeptidase (GGT), a membrane protein involved in recycling extracellular glutathione and regulating intracellular redox potential. Molecular associations between GGT and TM4 proteins **CD81**, CD53 and CD82, in addition to CD21 and CD19, were detected by co-precipitation and co-capping analysis. GGT is expressed on several B and T cell lines independently of CD21 expression. These results demonstrate that GGT is a component of widely distributed TM4 complexes, and that on B cells the GGT-containing TM4 complexes also contain CD19 and CD21.

3/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10040281 99030705 PMID: 9812906
Tetraspanin CD9 is associated with very late-acting integrins in human vascular smooth muscle cells and modulates collagen matrix reorganization.
Scherberich A; Moog S; Haan-Archipoff G; Azorsa D O; Lanza F; Beretz A
Laboratoire de Pharmacologie et Physiologie Cellulaires, Faculte de Pharmacie, Illkirch France.
Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) Nov 1998, 18 (11) p1691-7, ISSN 1079-5642 Journal Code: 9505803
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD9, a member of the tetraspanin family, and very late-acting (VLA) integrins are known to associate and form functional units on the surface of several cell types. We studied the changes in expression of CD9 and beta1-integrins (CD29, VLA) in human vascular smooth muscle cells (VSMCs) under in vitro culture conditions mimicking proliferative vascular diseases. We also investigated possible interactions between CD9 and VLA integrins in VSMCs. We found that CD9 is highly expressed in VSMCs and is subject to modulation, depending on the proliferative/contractile state of the cells. In the contractile phenotype, the levels of CD9, **CD81**, another tetraspanin, and CD29 are approximately 50% of those found in the proliferative phenotype. Coimmunoprecipitation experiments showed physical association between CD9 and CD29. CD9 was mainly associated with alpha2 and alpha3-integrins (CD49b and c) and also with alpha5-integrin to a weaker extent. Functionally, the addition of anti-CD9 monoclonal **antibodies** (MoAbs) doubled the extent of collagen gel contraction mediated by VSMCs, a model for the reorganization of the extracellular collagen matrix occurring in the vessel wall. Anti-CD29 MoAbs **inhibited** gel contraction, but anti-CD9 MoAbs counteracted this **inhibitory** effect of anti-CD29 MoAbs. Transfection of human CD9 into Chinese hamster ovary cells more than doubled the extent of Chinese hamster ovary cell-mediated collagen gel contraction (130% stimulation), confirming a role for CD9 in extracellular matrix reorganization. Thus, CD9 seems to be involved in the modulation of VLA integrin-mediated collagen matrix reorganization by VSMCs. These findings suggest that high CD9 expression is associated with a proliferative state of VSMCs. The role of CD9 could be to modulate the function of VLA integrins on the surface of VSMCs.

3/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10037036 99011351 PMID: 9794763
Binding of hepatitis C virus to **CD81**.
Pileri P; Uematsu Y; Campagnoli S; Galli G; Falugi F; Petracca R; Weiner A J; Houghton M; Rosa D; Grandi G; Abrignani S
IRIS, Chiron, Siena 53100, Italy.
Science (UNITED STATES) Oct 30 1998, 282 (5390) p938-41, ISSN

a laminin receptor, can affect cell motility and induce migration onto ECM substrates with which it is not engaged. By using DNA-mediated gene transfer, we expressed the human integrin subunit alpha 6A in murine embryonic stem (ES) cells. ES cells expressing alpha 6A (ES6A) at the surface dimerized with endogenous beta 1, extended numerous filopodia and lamellipodia, and were intensely migratory in haptotactic assays on laminin (LN)-1. Transfected alpha 6A was responsible for these effects, because cells transfected with control vector or alpha 6B, a cytoplasmic domain alpha 6 isoform, displayed compact morphology and no migration, like wild-type ES cells. The ES6A migratory phenotype persisted on fibronectin (Fn) and Ln-5. Adhesion **inhibition** assays indicated that alpha 6 beta 1 did not contribute detectably to adhesion to these substrates in ES cells. However, anti-alpha 6 **antibodies** completely blocked migration of ES6A cells on Fn or Ln-5. Control experiments with monensin and anti-ECM **antibodies** indicated that this **inhibition** could not be explained by deposition of an alpha 6 beta 1 ligand (e.g., Ln-1) by ES cells. Cross-linking with secondary **antibody** overcame the **inhibitory** effect of anti-alpha 6 **antibodies** , restoring migration or filopodia extension on Fn and Ln-5. Thus, to induce migration in ES cells, alpha 6A beta 1 did not have to engage with an ECM ligand but likely participated in molecular interactions sensitive to anti-alpha 6 beta 1 **antibody** and mimicked by cross-linking. **Antibodies** to the tetraspanin **CD81** **inhibited** alpha 6A beta 1-induced migration but had no effect on ES cell adhesion. It is known that **CD81** is physically associated with alpha 6 beta 1, therefore our results suggest a mechanism by which interactions between alpha 6A beta 1 and **CD81** may up-regulate cell motility, affecting migration mediated by other integrins.

3/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09559252 97477414 PMID: 9334370
Negative regulation of Fc epsilon RI-mediated degranulation by **CD81**
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Fleming T J; Donnadieu E; Song C H; Laethem F V; Galli S J; Kinet J P
Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, USA.
Journal of experimental medicine (UNITED STATES) Oct 20 1997, 186 (8) p1307-14, ISSN 0022-1007 Journal Code: 2985109R
Contract/Grant No.: AI/CA-23990; AI; NIAID; CA/AI-72074; CA; NCI; GM-53950; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Signaling through the high affinity receptor for immunoglobulin E (Fc epsilon RI) results in the coordinate activation of tyrosine kinases before calcium mobilization. Receptors capable of interfering with the signaling of antigen receptors, such as Fc epsilon RI, recruit tyrosine and inositol phosphatases that results in diminished calcium mobilization. Here, we show that **antibodies** recognizing **CD81** **inhibit** Fc epsilon RI-mediated mast cell degranulation but, surprisingly, without affecting aggregation-dependent tyrosine phosphorylation, calcium mobilization, or leukotriene synthesis. Furthermore, **CD81** **antibodies** also **inhibit** mast cell degranulation in vivo as measured by reduced passive cutaneous anaphylaxis responses. These results reveal an unsuspected calcium-independent pathway of antigen receptor regulation, which is accessible to engagement by membrane proteins and on which novel therapeutic approaches to allergic diseases could be based.

3/3,AB/33 (Item 33 from file: 155)

tyrosine phosphorylation. However, different cytoplasmic proteins were phosphorylated following triggering of either molecule. Taken together, the data demonstrate that **CD81** and HLA-DR antigens induce similar effector phenomena in the regulation of TNF-alpha release, homotypic aggregation and **inhibition** of JY cell proliferation.

3/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08567472 95325577 PMID: 7602090
CD82, member of the tetra-span-transmembrane protein family, is a costimulatory protein for T cell activation.
Lebel-Binay S; Lagaudriere C; Fradelizi D; Conjeaud H
Immunomodulation and Autoimmunity Laboratory, Rene Descartes University, Cochin Hospital, Paris, France.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jul 1 1995, 155 (1) p101-10, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is now well documented that full activation of T cells requires a two-signal triggering that can be mimicked, in the absence of accessory cells, by co-immobilization of mAbs directed to stimulatory/accessory molecules (CD2, CD3, CD28, adhesion molecules, etc.). In this report, we describe that engagement of CD82 can delivery such a costimulatory signal for full activation of the human T cell line Jurkat, leading to strong IL-2 production and cell differentiation. The CD82 Ag, which belongs to the new tetra-span-transmembrane family (CD9, CD37, CD53, CD63, and **CD81** (TAPA-1)), has been identified originally in our laboratory for its enhanced expression on three LAK-susceptible cell lines, and has been characterized as an activation/differentiation marker of mononuclear cells. Jurkat cells, stimulated in vitro by co-immobilization of anti-CD82 and anti-CD3 mAbs, produced high levels of IL-2, became strongly adherent to plastic dishes, and developed dendritic processes. These morphologic changes, associated with a total arrest of cell proliferation, were not the result of cell death but rather of cell differentiation, as shown by an increase in their metabolic activity. Costimulation through both CD82 and CD3 induced up-regulation of both IL-2 and IFN-gamma mRNA synthesis (but not of IL-4) and an increased expression of HLA class I molecules at the cell surface, which was **inhibited** by anti-IFN-gamma Ab.

3/3,AB/36 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13105148 BIOSIS NO.: 200100312297
Mechanism of hepatitis C virus-like particle-induced apoptosis in HUVEC.
AUTHOR: Munshi N(a); Ganju R K(a); Liang T Jake(a); Koziel M J(a); Groopman J E
AUTHOR ADDRESS: (a)Divisions of Experimental Medicine and Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA**USA
JOURNAL: Blood 96 (11 Part 1):p40a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Hepatitis C virus (HCV) infection causes inflammation of liver endothelium which contributes to the pathogenesis of chronic hepatitis. The mechanism of this endothelitis is not understood, since the virus does not appear to productively infect endothelial cells. We hypothesized an "innocent bystander" mechanism related to HCV proteins, and investigated whether the binding of HCV particles to human endothelium induced functional changes in the cells. Exposure of human vascular endothelial cells (HUVEC) to hepatitis C virus-like particles (HCV-LP) resulted in increased IL-8 production and induction of apoptosis. This programmed cell death appeared to be mediated by the Fas/Fas-L pathway as neutralizing **antibodies** for Fas and Fas-L significantly protected HUVEC against HCV-LP induced apoptosis. Treatment of HUVEC with HCV particles also enhanced Fas-L expression in these cells and augmented caspase-3 activation. This was confirmed by using a specific caspase-3 **inhibitor**, Z-DEVD-FMK. Neutralizing **antibody** to the **CD81** receptor showed that it participated in the HCV particle induced apoptosis of endothelial cells. Release of interleukin-8 did not appear to involve the **CD81** receptor, and IL-8 did not modulate apoptosis as shown by blocking its cognate receptors on HUVEC. These results suggest that HCV envelope proteins can trigger the release of inflammatory chemokines and endothelial apoptosis, and may explain the pathological finding of endothelitis.

2000

3/3,AB/37 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12913693 BIOSIS NO.: 200100120842
Retinal pigment epithelium express **CD81** (target of the antiproliferative **antibody**).
AUTHOR: Geisert E E Jr(a); Abel H J; Fan L; Geisert G R
AUTHOR ADDRESS: (a)Univ Of Tennessee Hlth Sci Ctr, Memphis, TN**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7062 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The present study focuses on the role of **CD81** (the target of the antiproliferative **antibody**,TAPA) in the regulation of the growth of retinal pigment epithelium (RPE). RPE were cultured from eight-day old rat pups. The level of **CD81** in the cultures was defined by immunoblot methods and the distribution of the protein was examined using indirect immunohistochemical methods. In addition, the effects of the **antibody** binding were tested in culture. **CD81** was found in all layers of the normal retina with a distinct lack of labeling in the inner and outer segments of the photoreceptors. Based on our original immunohistochemical analysis (Clarke and Geisert, 1998 Mol. Vision, http://www.molvis.org/molvis/v4/a3/), it was difficult to determine if **CD81** was expressed by RPE. By examining cultures of RPE we demonstrated that **CD81** was expressed on the surface of these cells and that it was concentrated at regions of cell-cell contact. When the AMP1 **antibody** (directed against the large extracellular loop of **CD81**) was added to cultured RPE the mitotic activity of the cells was depressed. Previous studies demonstrated that **CD81** was

expressed in retinal glia, the Muller cells which span the thickness of the retina, and astrocytes found in the ganglion cell layer. The present study demonstrated that **CD81** was also expressed by RPE. The dramatic effects of the AMP1 **antibody** and the location of **CD81** at regions of cell-cell contact support the hypothesis that this molecule is part of a molecular switch controlling contact **inhibition**.

2000

3/3,AB/38 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12869665 BIOSIS NO.: 200100076814
Intraparenchymal infusion of anti-TAPA/**CD81 antibodies** leads to functional recovery after spinal cord injury.
AUTHOR: Hamers F P(a); Dijkstra S; Lankhorst A J; Joosten E A; Bar P R; Gispen W H; Geisert E E Jr
AUTHOR ADDRESS: (a)Rudolf Magnus Institute for Neurosciences, University Medical Center, Utrecht**Netherlands
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-18617 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Modulation of the glial response to spinal cord injury may lead to enhanced functional recovery. The monoclonal **antibody** AMP1 was found to alter the stability of astrocyte-astrocyte contact in vitro and to **inhibit** proliferation of astrocytes and microglia. Furthermore, the AMP1 antigen (TAPA/**CD81**) is upregulated after traumatic spinal cord injury. Therefore we studied whether intralesional infusion of AMP1-mAb could enhance functional recovery after spinal cord contusion injury. Female Wistar rats were subjected to a moderate spinal cord contusion injury and implanted at the lesion site with a stainless steel cannula connected to an osmotic minipump. Two different doses of AMP1-mAb and one dose of pre-immune IgG were infused for 14 days. Neurological function was regularly assessed on several function tests for 8 weeks. The lower dose of AMP1 led to significantly better function on BBB (+-1.5 point) and Gridwalk tests as compared to the IgG control from 3 weeks onward. Hindpaw fine motor function, as assessed by BBB-subscores, was significantly better from 2 weeks onward. The higher dose of AMP1 did not differ from IgG control. These data suggest that AMP1 might be of value in the treatment of spinal cord injury, either by modulating the primary inflamatory process or by affecting the formation of the glial scar.

2000

3/3,AB/39 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11919586 BIOSIS NO.: 199900165695
Transmembrane 4 superfamily protein CD151 (PETA-3) associates with beta1 and alphaIIBbeta3 integrins in haemopoietic cell lines and modulates cell-cell adhesion.

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JOURNAL: Biochemical Journal 338 (1):p61-70 Feb. 15, 1999
ISSN: 0264-6021
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD151 (PETA-3/SFA-1) is a member of the transmembrane 4 superfamily (TM4SF) of cell-surface proteins and is expressed abundantly both on the cell surface and in intracellular membranes by the haemopoietic cell lines M07e, HEL and K562. In the presence of mild detergent (CHAPS), CD151 co-immunoprecipitated with integrin alpha4beta1, alpha5beta1, alpha6beta1 and alphaIIbbeta3. The association of CD151 with alpha4beta1 and alpha5beta1 seemed to be constitutive, as it was not modified by treatment of M07e cells with cytokines that regulate integrin function by 'inside-out' signalling. CD151 also associated with other tetraspans in an apparently cell-type-specific fashion, as defined by its co-precipitation with CD9, CD63 and **CD81** from M07e cells, but not from K562 cells, which express similar levels of these proteins. F(ab')2 fragments of monoclonal **antibodies** (mAbs) against CD151 caused homotypic adhesion of HEL and K562 cells that was dependent on energy and cytoskeletal integrity and was augmented in the presence of RGDS peptides. The adhesion was not blocked by function-**inhibiting** mAbs against beta1 or beta3 integrins, suggesting that cell-cell adhesion was not mediated by the binding of integrin to a cell-associated ligand. Furthermore, mAb CD151 did not affect adhesion of the cells to fibronectin, laminin, collagen or fibrinogen, which are ligands for alpha4beta1, alpha5beta1, alpha6beta1 and alphaIIbbeta3 integrins. Taken together, these results indicate that the ligation of CD151 does not induce the up-regulation of integrin avidity, but might act as a component of integrin signalling complexes.